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# EXPERIMENTAL OBSTRUCTIVE JAUNDICE

## ITS EFFECT ON FIBRINOGEN AND COAGULATION OF THE BLOOD

WALTER MOSS, M.D.
House Surgeon, Charity Hospital
NEW ORLEANS

The scientific explanation of the hemorrhagic tendency in patients suffering with jaundice has been energetically sought for by a great number of investigators, some of whom are apparently definitely convinced by the results of their experimental work that the problem is settled. It is difficult for one reviewing the literature to come to any definite conclusion in his own mind relative to this phenomenon, because of the wide diversity of opinions and because of the conflicting data in the literature.

The fibrinogen content of the blood plasma has not been investigated carefully from an experimental standpoint as a possible cause for this hemorrhage, and it was with that in mind that the work herein submitted was done in an attempt to arrive at some solution of this perplexing and vexing problem.

After considering this subject theoretically, it seems that the hemorrhagic tendency in these patients might be attributed to the presence of abnormal amounts of fibrinogen, which plays such a prominent rôle in the coagulation of the blood. It is conceded that the greater part of the blood fibrinogen has its origin in the liver, and the fibrinogen content of the plasma has been shown to vary with conditions of the liver. It is assumed, of course, that obstruction to the outflow of bile by the normal route causes more or less hepatic damage.

The restoration of fibrinogen to its normal level in the blood after depletion from any cause, e. g., bleeding, is almost exclusively accomplished by the liver, as was indicated by Howe.[1] Mann and Bollman[2] demonstrated that following complete extirpation of the liver the fibrinogen of the blood did not return to its normal level after bleeding. Recent investigations, particularly those of Howe,[3] point to the liver as the main source of supply of fibrinogen.

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From the Department of Surgery, Tulane University.

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1. Howe: J. Biol. Chem. **57**:235 (Aug.) 1923.
2. Mann and Bollman: Proc. Staff Meet., Mayo Clin. **4**:328 (Nov.) 1929.
3. Howe: Physiol. Rev. **5**:439, 1925.

Whipple attributed the origin of fibrinogen to the liver. Foster and Whipple [4] found that the fibrinogen content of the plasma is reduced by measures that cause destruction of hepatic tissue. McMaster and Drury [5] further confirmed the fact that fibrinogen is of hepatic origin. The blood of normal animals was defibrinated and reinjected, and it was found that 90 per cent of the normal fibrinogen content was present in six hours. When hepatectomized animals were treated in the same way, there was noted a slight rise of fibrinogen in from four to five hours, presumably from a reserve in the tissues, but after from four to five hours the fibrinogen content decreased until death. It was concluded that without the liver the organism apparently has no power to regenerate fibrinogen.

On the basis of the aforementioned results and similar personal observations, Full,[6] McLester [7] and many others concluded that the fibrinogen content of the plasma may be used as an index to hepatic function. Peters and Van Slyke [8] contended that decrease in fibrinogen content does not parallel the degree of destruction of the liver. They admitted, however, that severe injury to the liver is, in a number of cases, attended with decrease in plasma fibrinogen. Foster and Whipple [4] showed that inflammatory and destructive lesions of the liver cause an increase in fibrinogen as would a normal stimulus. When the loss of liver substance is so great that the organ can no longer meet the demands of the body, fibrinogen decreases.

Wiener and Wiener [9] conceded that changes in the permeability of the endothelium may be responsible for, or may influence, the change in concentration of fibrinogen in the plasma. Peterson assumed that the capillaries govern permeability by highly specialized function. Their endothelial walls act as an "ultrafilter," and any changes in their structure should result in altered concentrations of the various materials that are allowed to pass. Permeability of the capillaries depends on permeability of the endothelial cells in the walls of the vessels. An increase in this permeability may be caused by dilatation from physical, nervous or chemical stimuli (Krogh [10]) and by increased

4. Foster and Whipple: Am. J. Physiol. **58**:407, 1922.

5. McMaster and Drury: Proc. Soc. Exper. Biol. & Med. **26**:490, 1929.

6. Full: Verhandl. d. Kong. f. inn. Med. **33**:201, 1921.

7. McLester: Diagnostic Value of Blood Fibrin Determinations with Special Reference to Disease of the Liver, J. A. M. A. **79**:17 (July 1) 1922.

8. Peters and Van Slyke: Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1931.

9. Wiener and Wiener: Plasma Proteins, Arch. Int. Med. **46**:236 (Aug.) 1930.

10. Krogh: Anatomy and Physiology of Capillaries, New Haven, Conn., Yale University Press, 1923, p. 230.

capillary pressure or injury (Landis [11]). The viscosity of fibrinogen is known to be greater than that of the serum proteins, and the permeability of hepatic endothelium is said to be greater than that of any other endothelium. Wiener and Wiener,[9] after an exhaustive study of fibrinogen and serum proteins in man, concluded that the physiologic limits of the concentration of fibrinogen in the plasma are at wide variance. Their reports, from investigation of the amounts of these substances in various physiologic and pathologic conditions, show that the fibrinogen is slightly increased during menstruation and definitely increased during the later months of pregnancy and during the puerperium. They concluded further that any irritation of the liver, i. e., slight infections, exposure to the x-rays, ingestion of chloroform and phosphorus in small doses and all inflammatory processes, produces an increase in the fibrinogen content of the plasma. In cirrhosis of the liver, they found a slight increase early in the process, but a decrease or low normal fibrinogen content later, whereas concurrent infections elsewhere in the body caused only slight increases. In the presence of jaundice without pyrexia, the concentration of fibrinogen was found to be within normal limits. In cholecystitis, the findings are similar to those in infections. Pickering [12] also noted a definite decrease in fibrinogen content of the plasma in cases of cirrhosis of the liver. Whipple and Hurwitz [13] showed that small doses of chloroform and phosphorus increase the coagulability of the blood and increase the fibrinogen content of the plasma, but that large doses of these "liver poisons" produce the opposite effect.

There has been a great deal of controversy among investigators in the clinical field, as well as among those in the experimental laboratory, concerning the cause of hemorrhage in jaundiced patients. Most of the work that has been done has been to determine whether or not fluctuation in the calcium content of the serum occurs, and whether or not these changes affect coagulability of the blood in jaundiced patients.

In reviewing the literature it is difficult, because of the vast difference in opinions, for one to obtain any established facts concerning the effect that calcium content of the blood has on coagulability. These opinions are based on results obtained in the clinic and the laboratory; thus it is impossible to conclude that any constant relationship exists. Halverson, Mohler and Bergeim [14] reported a slight reduction in calcium

11. Landis: Am. J. Physiol. **81**:124, 1927.

12. Pickering: The Blood Plasma in Health and Disease, New York, The Macmillan Company, 1928, p. 24.

13. Whipple and Hurwitz: J. Exper. Med. **13**:136, 1911.

14. Halverson; Mohler, and Bergeim: Calcium in the Blood in Tuberculosis, J. A. M. A. **68**:1309 (May 5) 1917.

content of blood serum in jaundice. The reduction noted was considered more apparent than real. Koechig [15] arrived at the same conclusion. Walters and Bowler,[16] Snell, Greene and Rowntree [17] and Zimmerman [18] found no change in serum calcium in obstructive or other types of jaundice. Kirk and King [19] reported moderate reductions in total calcium, but greater reductions in diffusible calcium, emphasizing the importance of the rôle that the diffusible, or ionizable, calcium plays in coagulation. Emerson [20] corroborated the findings of Kirk and King by a series of experiments, and called attention to the fact that the probable source of error obtained by other investigators was the disregard of the effect of ether anesthesia. He demonstrated that specimens of blood taken during or shortly after ether anesthesia show an increase in calcium content of the serum. The experimental results obtained by Emerson are not fraught with this error. He showed that in jaundice the serum calcium is diminished concomitantly with diminished coagulability of the blood, and he was able to restore calcium to the normal level by administration of calcium salts in therapeutic doses. Emerson also found an increase in serum calcium in animals with biliary fistulas. Buchbinder and Kern [21] found no alteration in serum calcium after ligation of the common bile duct of the adult dog, but a progressive decrease after the same procedure in the puppy. Subsequently, these same authors found that, after producing obstructive jaundice in thyroparathyroidectomized animals, there resulted a diminution or an absence of tetany. The period of survival of the animals suffering with tetany was prolonged if the jaundice was maintained over a considerable length of time. If, after removal of the parathyroid glands, the animals were subjected to "acute" jaundice, they suffered with severe and terminal tetany. The conclusion was drawn that tetany was altered by obstructive jaundice, on the basis of (1) the response of the thyroparathyroidectomized animal, (2) the relief from tetany following intravenous injection of bile and (3) the absence of tetany in late obstructive jaundice in the puppy with calcium at the tetanic level. One is here reminded of the action of bile as a depressant of the central

15. Koechig: J. Lab. & Clin. Med. **9**:679 (July) 1924.

16. Walters and Bowler: Surg., Gynec. & Obst. **39**:200 (Aug.) 1924.

17. Snell; Greene, and Rowntree: Diseases of the Liver: Comparative Study of Certain Tests for Hepatic Function in Experimental Obstructive Jaundice, Arch. Int. Med. **36**:273 (Aug.) 1925.

18. Zimmerman: Am. J. M. Sc. **174**:379 (Sept.) 1927.

19. Kirk and King: J. Lab. & Clin. Med. **11**:928 (July) 1926.

20. Emerson: J. Lab. & Clin. Med. **14**:122 (Nov.) 1928.

21. Buchbinder and Kern: Experimental Obstructive Jaundice: II. Modification of the Parathyroid Tetany Mechanism in Jaundice, Arch. Int. Med. **41**:754 (May) 1928.

nervous system; i. e., it raises the threshold of nervous excitability. Snell and Greene [22] emphasized the fact that there is no agreement concerning the variation in the calcium content of the serum in jaundice. They found that in jaundice all the fractions of the serum calcium—the total, the nondiffusible and the diffusible—are equally affected. They concluded that the amount of alteration in the diffusible calcium of jaundiced patients is not significant. The coagulation time was not considered by Snell, Greene and Rowntree, but they expressed the belief that it is affected by calcium in some more complicated mechanism rather than directly. The variation in dogs and patients was reported insignificant. Gunther and Greenberg [23] stated that a review of the literature produced no proof of a deficiency of available calcium in the blood of jaundiced patients, nor any direct proof of a deficiency of diffusible calcium in the serum. They observed in jaundiced patients a diminution in the nondiffusible calcium, but parallel with this was a loss of serum albumin accounted for by a decrease in total serum proteins. They contended that this cannot be interpreted as an indication of a deficiency of available calcium. They found that the concentration of nondiffusible calcium was low in a few patients with jaundice, but that there was an accompanying lowered concentration of serum albumin, and that the concentration of neither serum albumin nor nondiffusible calcium fluctuated with the degree of jaundice. The nondiffusible fraction of serum calcium was considered to be low as a result of the low serum albumin. It was shown that the value of diffusible calcium is a more accurate measure of the physiologically available calcium than the value of either the nondiffusible or the total calcium fraction in the serum. Gunther and Greenberg contended that factors other than alteration in the amount of available calcium must be sought for to explain satisfactorily abnormal bleeding in jaundiced patients. Waltman Walters,[24] recently, in an excellent treatise on obstructive jaundice, presented evidence to the effect that calcium, given in therapeutic dosage, is rapidly excreted by the kidneys. It does not accumulate in the blood, and the normal level of the serum calcium is restored in two hours.

Ravdin, Riegel and Morrison [25] compared the relative merits of calcium and dextrose as hemostatic agents in the presence of jaundice, and agreed with Bancroft, Kugelmass and Stanley-Brown [26] that coagu-

22. Snell and Greene: Am. J. Physiol. **92**:630 (April) 1930.

23. Gunther and Greenberg: I. The Diffusible Calcium and the Proteins of the Blood Serum in Jaundice, Arch. Int. Med. **45**:983 (June) 1930.

24. Walters, Waltman: Obstructive Jaundice: Physiological and Surgical Aspects, Rochester, Minn., Mayo Foundation, University of Minnesota, 1931.

25. Ravdin; Riegel, and Morrison: Ann. Surg. **91**:801 (June) 1930.

26. Bancroft; Kugelmass, and Stanley-Brown: Ann. Surg. **90**:161, 1929.

lation and bleeding times are of little value in determining a hemorrhagic tendency. They claimed that, in spite of the agitation favoring the use of calcium in cases of obstructive jaundice, no one has clinically demonstrated a deficiency of serum calcium in these cases. Dextrose is used, and it was suggested that it may help in restoration and repair of the damaged liver. They cited Minot and Cutler's [27] demonstration of the beneficial effect of the use of calcium in dogs with hepatic degeneration, in the blood of which there occurred, as a result of this disease, an increase in guanidine and like substances. They took issue with Partos and Svec [28] in their contention that hyperglycemia results from the use of calcium, on the ground that it does not occur consistently. Nevertheless, they found that calcium therapy was efficacious in diminishing the damage to the liver produced by biliary obstruction. Schreiber [29] and Kehr [30] suggested the use of dextrose preoperatively in cases of jaundice. Since 1920, the use of this substance has become widespread. Walters [31] and Whipple [32] advocated the use of dextrose and calcium and considered dextrose of primary importance as regards the reduction of mortality from surgical operations. Davis, Hall and Whipple [33] asserted that a diet high in carbohydrate would affect regeneration of hepatic tissue at the rate of 100 Gm. daily. Ravdin et al.[25] stated that a diet high in carbohydrate causes more rapid restoration of hepatic structure after release of biliary obstruction and exerts a definitely favorable effect while obstruction exists. They stated that clinical patients whose blood has a prolonged clotting time have severe hepatic damage. Mann, Bollman and Markowitz [34] showed in hepatectomized animals that there occurs: (1) a variable change in coagulation of the blood; (2) a diminution of fibrinogen content, after depletion of the latter from hemorrhage, with partial or no restoration of the same, and (3) no parallelism between fibrinogen content and coagulability of the blood. The latter point was confirmed by work on normal and jaundiced dogs by Ravdin, Riegel and Morrison.[25] Minot and Cutler [27] demonstrated in dogs an increase in guanidine content of the blood associated with hypoglycemia in the presence of jaundice. Ellis [35] showed that

27. Minot and Cutler: Proc. Soc. Exper. Biol. & Med. **26**:607, 1929.
28. Partos and Svec: Arch. f. d. ges. Physiol. **218**:209, 1930.
29. Schreiber: Zentralbl. f. Chir. **2**:1200, 1913.
30. Kehr: Ergebn. d. Chir. u. Orthop. **8**:471, 1914.
31. Walters: Surg., Gynec. & Obst. **33**:651, 1921.
32. Whipple: S. Clin. North America **1**:373, 1921.
33. Davis; Hall, and Whipple: The Rapid Construction of Liver Cell Protein on a Strict Carbohydrate Diet Contrasted with Fasting: Mechanism of Protein-Sparing Action of Carbohydrate, Arch. Int. Med. **23**:689 (June) 1919.
34. Mann; Bollman, and Markowitz: Am. J. Physiol. **90**:445, 1929.
35. Ellis: Biochem. J. **22**:353 and 930, 1928.

dextrose protects the experimental animal from toxemia due to guanidine, definitely proving that it is of value in a restorative rôle. Partos and Svec [28] proved that substances which increase the coagulability of the blood mobilize glycogen and produce hyperglycemia, and that substances prolonging the coagulation time cause hypoglycemia. Cannon and Gray [36] showed that epinephrine causes increase in blood sugar and increase in coagulability of the blood. Rabinovich [37] demonstrated that the coagulation time was diminished following anesthesia, and emphasized the fact that during the first fifteen minutes of anesthesia the blood sugar increases. Boldyreff,[38] followed by Turcatti,[39] expressed opinions opposite to these. Boldyreff stated that with complete loss of pancreatic secretion there is a rise in blood sugar with diminution in coagulability of the blood. Ravdin, Riegel and Morrison [25] stated that hyperglycemia does not increase the coagulability of the blood in all cases, but that hyperglycemia and increase in the coagulability of the blood are present in a great many cases. They suggested that dextrose has the effect of stimulating the formation of fibrinogen, but their experimental data do not bear out this assumption. Svec [40] injected insulin into experimental animals, producing hypoglycemia, which was followed by diminution in coagulability of the blood. Partos [41] confirmed these results, and showed that diabetic animals had increased coagulability of the blood. He was able to produce similar effects by administration of epinephrine hydrochloride to one series of depancreatized dogs and morphine to another series. Walters [24] stated that he considers the preoperative administration of dextrose to be of extreme importance in these cases. He also favors small doses of calcium chloride (5 grains [0.32 Gm.]), intravenously, for three days prior to operation.

Heparin has been investigated in Howell's laboratory. Howell [42] said that diminution of the heparin in the blood is probably the cause of bleeding in hemophilia, jaundice and other such pathologic conditions. This cannot be proved, however, until a method has been devised for quantitative estimation of heparin. Heparin is present in the blood in such small quantities that it is difficult to obtain it even qualitatively. Up to the present time there has been no method submitted for its quantitative determination.

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36. Cannon and Gray: Am. J. Physiol. **34**:232, 1914.
37. Rabinovich: Brit. J. Exper. Path. **8**:343, 1927.
38. Boldyreff: Am. J. M. Sc. **177**:778, 1929.
39. Turcatti: Compt. rend Soc. de biol. **100**:116, 1929.
40. Svec: Arch. f. d. ges. Physiol. **224**:62, 1930.
41. Partos: Arch. f. d. ges. Physiol. **224**:448, 1930.
42. Howell: Am. J. Physiol. **77**:689 (Aug.) 1926.

Howell and Holt [43] showed that heparin does not react with calcium salt, but that there is a thermolabile substance in the blood that reacts with the heparin to form antithrombin. This thermolabile substance can be destroyed by raising the temperature of the blood to 70 C., whereas heparin is not destroyed at 100 C. These authors expressed the belief that heparin is present in the blood under normal conditions. They contended that it is an activator for pro-antithrombin, preventing the formation of thrombin in the normal circulation. By this mechanism, the fluidity of the blood is maintained in the undisturbed vascular system. Heparin also prevents the activation of prothrombin to thrombin, according to Howell and Holt.[43] Thus, by means of a double mechanism, this substance is responsible for the prevention of intravascular clotting. Howell [42] expressed the belief that the presence of an abnormal amount of heparin may be responsible for the hemorrhagic tendency of patients with hemophilia and jaundice.

Howell,[44] in a still later publication, again claimed for heparin all the possibilities for which he contended in the previous article. He showed that it was increased in the blood by intravenous injection of peptone. He also found that in shed blood its action was neutralized by the phosphatid material furnished by the corpuscles or tissue cells. Howell found that the antithrombin is increased by intravenous administration of heparin.

Stuber and Lang [45] stated that heparin inhibits coagulation of the blood by inhibition of glycolysis. They observed that, following its injection, there was a decrease in coagulability of the blood, along with a decrease in glycolysis.

The tissue extracts and their place in the coagulation process have been thoroughly investigated by Mills.[46] The first attempts made at isolation of their thromboplastic elements were made by Wooldridge,[47] who found that the thromboplastic action of these extracts is due to a phospholipin, which, he determined, was a lecithin. In Howell's laboratory this was found to be cephalin (Mills). Mills [46] demonstrated that it is present in all organs but to a greater extent in the lung. He contended that, in addition to the phospholipoid material, the presence of the protein component of the tissue extracts is necessary for the manifestation of the maximum potency of the thromboplastic agents. The intravenous injection of phospholipin and the protein component of the tissues produces intravascular clotting and death.

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43. Howell and Holt: Am. J. Physiol. **47**:328, 1919.

44. Howell: Am. J. Physiol. **71**:553 (Feb.) 1925; Bull. Johns Hopkins Hosp. **42**:199 (April) 1928.

45. Stuber and Lang: Biochem. Ztschr. **212**:16, 1929.

46. Mills: J. Biol. Chem. **40**:425 (Dec.) 1919.

47. Wooldridge, L. C.: On Chemistry of the Blood and Other Scientific Papers, London, Kegan Paul, Trench, Trübner & Co., 1893.

## EXPERIMENTAL WORK

In selecting animals for this experimental work, it was decided that dogs would be most suitable. The biliary system of the dog is quite similar to that of man.

The greatest difficulty confronting one, in producing experimental obstructive jaundice in dogs, is the presence of accessory bile ducts. Occasionally, one or more hepatic ducts empty directly into the duodenum. Rarely, there is a duct from the gallbladder opening into the duodenum. It is necessary to interrupt every channel carrying bile from the liver in order to produce jaundice that will persist. There are so many branches joining the various bile ducts that the duct or ducts, overlooked at one operation, following which the jaundice subsides, are found at the time of the second operation to be enormously dilated. These enlarged channels apparently are sufficient to allow passage of the noxious bile to the duodenum. In the course of two or three days the stagnation is relieved and the jaundice disappears.

Dogs suffering with obstructive jaundice succumb within a relatively short period of time. Therefore, few of the observations are made in the presence of long-standing cholemia.

Twenty-seven animals were subjected to acute obstructive jaundice. The common bile duct and accessory ducts, when present, were divided between ligatures. On the third or fourth day each dog suffered with jaundice that could be recognized clinically. There was an icteric discoloration of the conjunctivae and skin. The feces became putty-colored or clay-colored and typically acholic, and biliuria was present. The dogs were perceptibly ill, and severe toxemia was evident.

Six of the dogs died before biliary obstruction had begun to produce a marked effect. One dog died on the operating table, as the result of pulmonary collapse. There was a diaphragmatic hernia on the right side, with the spleen, omentum and one lobe of the liver in the right pleural cavity. As this hernia was reduced, collapse of both lungs occurred. A rent was found in the mediastinal pleura, probably secondary to collapse of the right lung. Collapse of the left lung followed. Another animal died the day following operation. The cause of death was given as asthenia. Probably operative trauma played its part here, too, as the duct was located and ligated with considerable technical difficulty. Three dogs suffered evisceration and succumbed as the result of self-mutilation, followed by hemorrhage One died three days after operation, the cause of death undetermined. One dog with jaundice died on the eighth day; the cause of death was pneumonia.

Fifteen of the twenty-one animals that lived to show the effects of biliary obstruction died early, the average length of life being 15.7 days. Of the number (twenty-one) that survived to develop jaundice,

twenty-one (100 per cent) died of diffuse hepatitis, the average length of life being 31.6 days. The livers in gross, both on the surface and on section, showed areas of destruction, which were bile-stained. The peritoneum and all viscera were bile-stained.

Determinations of the fibrinogen in the blood plasma were made at intervals during the disease. The Wu method[48] was used. This method may be used with impunity, if one attempts to determine fibrinogen for comparative analysis, as was done in approaching this problem. The figure given by Wu for the tyrosine equivalent for the human being was 16.4. This was calculated on an average of only two determinations, 16 and 16.8, as given in the original publication. It may be realized that, even with the difference of 0.8 in these figures, there exists a considerable variation, and that the percentage of error is not to be overlooked. The tyrosine equivalent for dogs (17.1) was derived from an average of twenty-four normal determinations. There was considerable variation in the different figures that were determined, and an average of these was used. The percentage variation in the end-results was not greater than the percentage variation of the figures for the tyrosine equivalent. Thus the figure, as stated, should hold as a fair multiplicand in the calculation of the fibrinogen values for use on a comparative basis.[49]

In determining the tyrosine equivalent for the dog, twenty-four determinations were made. The values varied from 12.5 to 19.7, and the range of error is rather wide for one to consider using the method without reservation for exact determinations of the fibrinogen content of plasma. It may be added that, in making the last twelve determinations, great care was exercised, and on the filtrate from each specimen two determinations of both nitrogen and tyrosine were made as a check; it was found that the greatest variation in these figures was negligible when the final equivalent figure was calculated.

A table of the averages of the percentage increases in fibrinogen content of the plasma on successive days, with the number of animals on which determinations of this plasma component were made, is appended (table 1). The figure given represents the percentage increase above the normal for each dog.

An average was made of the fibrinogen determinations of each week. The percentage increase (above the average of the normal fibrinogen content for the twenty-seven dogs) for each week was calculated (table 2).

It is evident from the analysis of table 2 that there is a constant increase in the fibrinogen content of the plasma from week to week in

48. Wu: J. Biol. Chem. **51**:33 (March) 1922.
49. Bliss, Sidney W.: Personal communication.

experimental obstructive jaundice. One must keep in mind, however, that relatively few determinations were made during the fourth week, for reasons that have been given.

The LaMotte-Pigford colorimetric method was used for determination of the icterus index.

The average of the determinations of the icterus index on the dogs before operation was 1.9 units. There was a gradual increase in the

TABLE 1.—*Average Percentage Increase of Fibrinogen in Plasma in Experimental Obstructive Jaundice*

| Day | Percentage Increase | Number of Animals |
|---|---|---|
| 3d | 33 | 3 |
| 4th | 16 | 8 |
| 5th | 63 | 13 |
| 6th | 60 | 4 |
| 7th | 11 | 4 |
| 8th | 27 | 10 |
| 9th | 37 | 2 |
| 10th | 66 | 3 |
| 11th | 50 | 6 |
| 12th | 69 | 1 |
| 13th | 13 | 3 |
| 17th | 12 | 1 |
| 18th | 62 | 6 |
| 19th | 38 | 1 |
| 20th | 57 | 2 |
| 22d | 72 | 1 |
| 24th | 78 | 1 |
| 25th | 58 | 1 |
| 29th | 16 | 2 |
| 31st | 74 | 2 |
| 32d | 12 | 1 |
| 33d | 52 | 1 |

TABLE 2.—*Average Weekly Percentage Increase of Fibrinogen in Plasma in Experimental Obstructive Jaundice*

| Week | Percentage Increase | Number of Animals |
|---|---|---|
| 1st | 44 | 29 |
| 2d | 46 | 29 |
| 3d | 53 | 10 |
| 4th | 62 | 4 |

average up to the eighth day. After the eighth day, there began a fluctuation that was not regular. The icterus index varied from 3 to 75 units after the initial increase. During the first, second, third, fourth and fifth weeks, the averages of the icterus indexes were 27, 28, 21, 17 and 35 units, respectively. Whereas the average for the first week was rather low, the highest figures of this determination were consistently noticed in the last two or three days of that week. The average for the fifth day was 26 units; for the sixth day, 32 units; for the seventh day, 52 units. There was a general decrease in the icterus

in the second week, but it was apparently more constant at this time, only varying from 20 to 36 units. During the third week, the icterus index approximated 20 units; during the fourth week, the average was 17 units, and during the fifth week, 35 units.

The coagulation time was estimated by means of the Brodie-Russell-Boggs coagulometer.

It was found that the average normal coagulation time of the twenty-seven dogs was 1 minute and 32 seconds. The coagulation time was

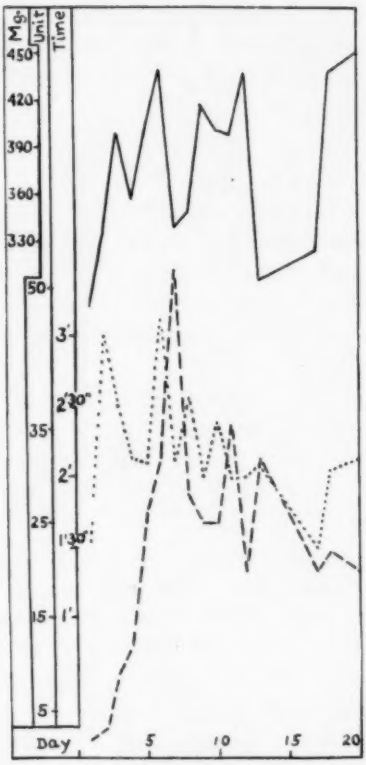


Fig. 1.—This and the graphs in figures 2, 3, 4 and 5 show the variations in fibrinogen content of the blood plasma, coagulation time and icterus index in experimental obstructive jaundice. The solid line represents the fibrinogen content of the plasma in milligrams; the dotted line, the coagulation time in minutes and seconds, and the broken line, the icterus index in units. In this graph are represented the daily averages of these determinations on all of the animals.

found to be consistently increased throughout the experiment, but not in a regular manner. However, the averages for the first, second, third, fourth and fifth weeks were 2 minutes and 35 seconds, 2 minutes and 10 seconds, 1 minute and 54 seconds and 2 minutes and 25 seconds, respectively.

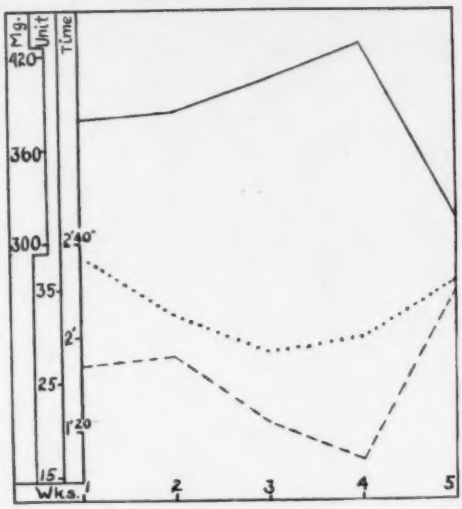


Fig. 2.—Weekly averages of the determinations of fibrinogen, coagulation time and icterus index of all the animals.

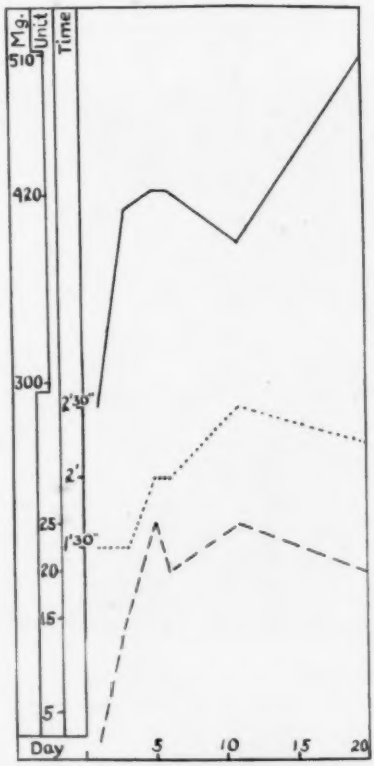


Fig. 3.—Record of variations in the determinations for typical animal 1.

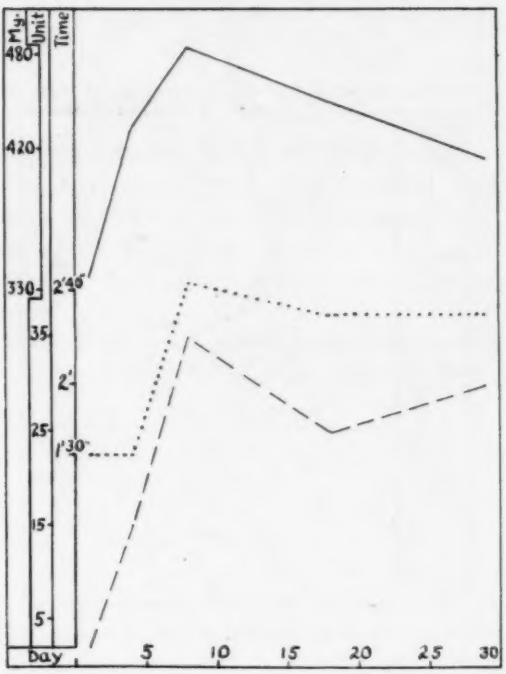


Fig. 4.—Record of variations in the determinations for typical animal 2.

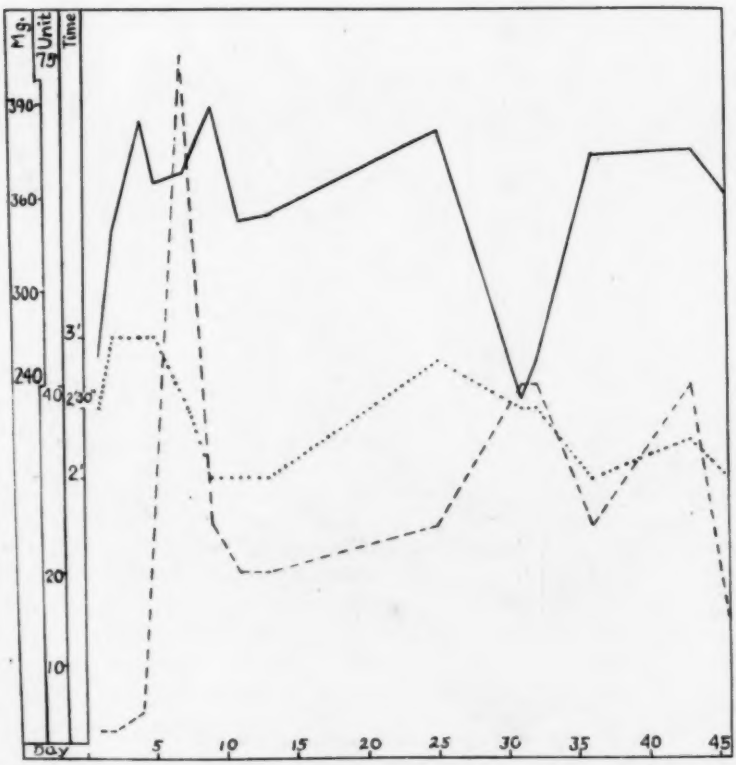


Fig. 5.—Record of variations in the determinations for the animal that survived the operation for the longest period.

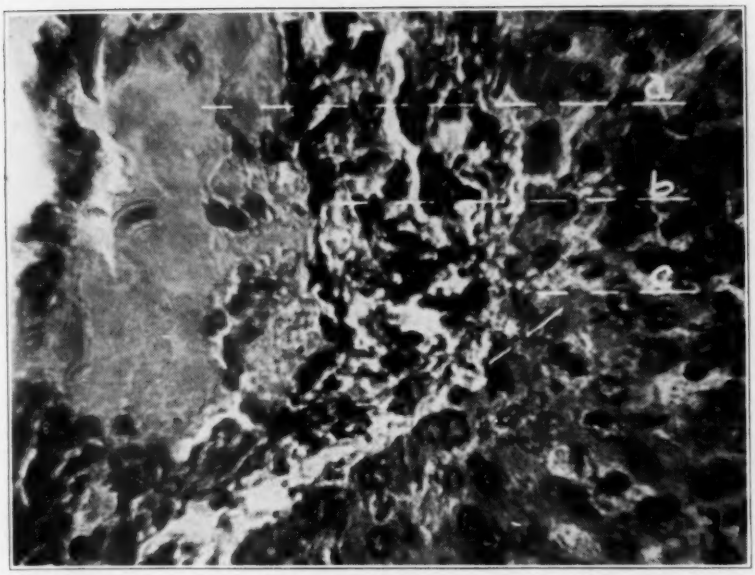


Fig. 6.—Damaged liver in experimental obstructive jaundice (under high power magnification), showing (*a*) hyalin-like material, (*b*) beginning cirrhosis and (*c*) hepatic necrosis at the periphery. The hepatic parenchyma in this slide was seen to be decidedly damaged.

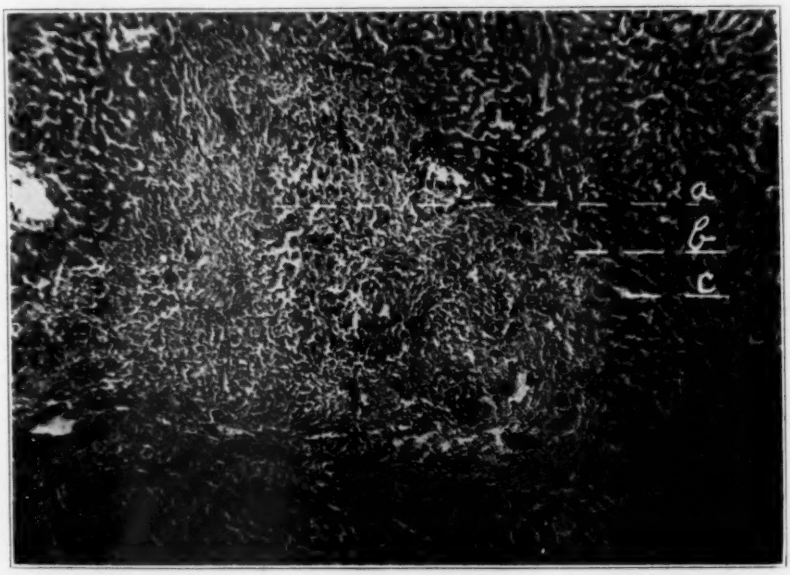


Fig. 7.—Damaged liver (low power) showing (*a*) fibrous connective tissue, (*b*) areas of hepatic cells undergoing degeneration and (*c*) cells of parenchyma unchanged. These areas, representing the third stage, are much larger than those in either of the two previous stages. The fibrous connective tissue has replaced the hyaline material, except for a few small areas.

PATHOLOGY

As has been stated, the primary cause of death of most of the animals could be attributed only to hepatic degeneration. The livers presented areas of destruction, which were apparent on the surface and on gross section, and which were bile-stained. These areas varied in diameter from 1 mm. to 3 or 4 cm.

The microscopic sections of the livers of the animals that had suffered from the mildest degree of jaundice showed a definitely disarranged hepatic parenchyma in the lobules, but a very small degree of destruction of the cells per se.

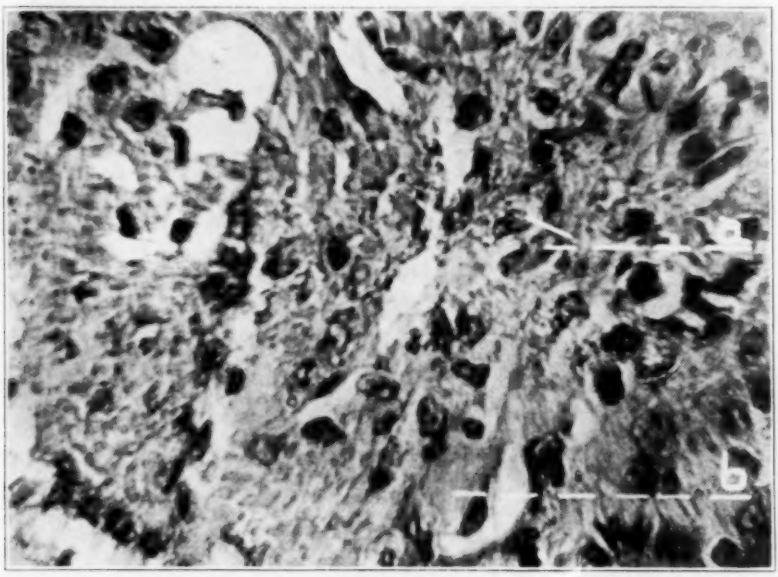


Fig. 8.—Damaged liver (high power) showing (*a*) fibroblasts and (*b*) hyaline material. There is seen complete replacement of hepatic parenchyma, and only a few areas of hyaline material remain.

A further lesion, which may be divided into three stages, was observed. These consisted of: 1. Small areas of necrosis, which were infiltrated by leukocytes, the lymphocyte being the predominating cell; polymorphonuclear leukocytes were only occasionally observed. These areas studded the parenchyma throughout, and because of the types of cells found were classified as subacute inflammatory processes. 2. Larger areas than these, including the same cellular elements but, in addition, a hyalin-like material, which predominated (fig. 6). 3. Areas, even larger than those classified under 2, in which cirrhosis was observed, a proliferation of fibrous connective tissue (figs. 7 and 8).

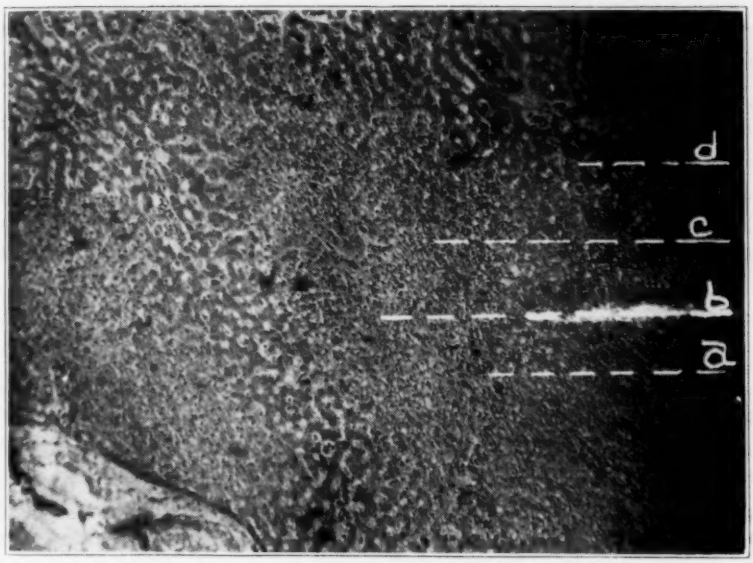


Fig. 9.—Damaged liver (low power) showing (*a*) central vein of lobule, (*b*) hepatic necrosis, (*c*) areas of fatty degeneration and (*d*) normal hepatic cells at periphery of lobule. In this photomicrograph are represented areas of central necrosis in the lobule. The cells at the periphery are unaffected. This shows the changes that took place in the livers of most of the animals.

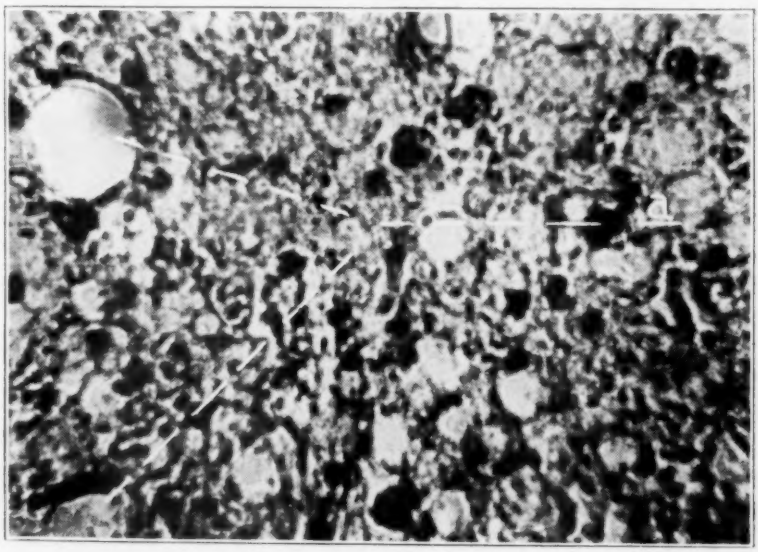

Fig. 10.—Areas of fatty degeneration (*a*) under high power magnification.

Central necrosis of the lobules was present in the greatest number of the animals. This lesion consisted of fatty degeneration (figs. 9 and 10). It was more pronounced in the central part of the lobule for two reasons: first, because the cells in the center of the lobule were the more constantly bathed by the bile, and second, because their blood supply was directly affected owing to injury to the hepatic vessels. The cells at the periphery were unchanged owing to the unimpaired blood supply, the result of an intact portal system and because the bile could be transported more readily from this area for the same reason.

## COMMENT

It is evident from the results obtained that no parallelism exists between the fibrinogen content of the blood and the degree of icterus. However, the fibrinogen content of the plasma was high in the first week following obstruction of the extrahepatic bile ducts. The icterus index and coagulation time were also increased during the first week. The fibrinogen content continued to increase during the second and third weeks, whereas the icterus index and coagulation time either decreased or remained stationary. The results obtained during the fourth and fifth weeks are not dependable, because of the fact that comparatively few determinations were made during this stage of the condition.

The increase in the fibrinogen content and the coagulation time during the first week might be considered as the result of the operation, but it is evident that the greatest percentage increase above normal occurred on the fifth day. It seems reasonable that after the first day or so the effect of the operation can be dismissed as a factor in causing this increase. Hueck [50] observed that the fibrinogen content of the plasma was increased after operation.

The results of this experiment have shown that bile is an irritant to the liver and in obstructive jaundice is a stimulus to the formation of more fibrinogen by the liver as is acute inflammation, thus corroborating the results of Wiener and Wiener. It is agreed that this is probably also due to the increase in the permeability of the hepatic endothelium.

It is found that the fibrinogen content of the blood increased considerably just before death, which might be attributed to concentration of the plasma by dehydration.

The fluctuation of the coagulation time is found to coincide with that of the degree of icterus. This was observed in a great majority of the individual animals (figs. 1 and 2). The increase in the icterus indexes is self-explanatory. Following the obstruction in the

50. Hueck: Arch. f. klin. Chir. **136**:627 (Aug.) 1925.

biliary system the normal exit for the bile was blocked. One is justified in assuming that the reason the icterus decreased after the first week was that a diminution in the amount of bile produced by the liver had occurred, owing to destruction of liver cells.

## SUMMARY AND CONCLUSIONS

An attempt has been made to determine whether or not some relationship exists between the fibrinogen content of the plasma, the degree of icterus and the coagulation time of the blood in obstructive jaundice. If some definite relationship exists among these factors, it is reasonable to suppose that it would be enlightening as to the cause of hemorrhage in the presence of jaundice.

It must be stated that as yet there is no adequate proof that any one factor is responsible for this hemorrhage.

Deficiency of calcium in the serum should not be considered as a causative factor in the production of hemorrhage in obstructive jaundice. The results of investigations reported in the literature indicate that a deficiency of calcium is not constant in jaundice, nor is it directly implicated in prolonging the coagulation time.

The contention favoring heparin as a cause for this bleeding is not substantiated by clinical or experimental proof. Little is known of the presence of heparin in the blood, and one can only theorize as to what factors influence the fluctuation of the quantity of heparin present in the circulating blood. The present investigation demonstrates that bile causes destruction of hepatic parenchyma, and the possibility that heparin is increased in the blood in obstructive jaundice is admitted.

It is concluded from this experimental work that the fibrinogen content of the plasma is not decreased in experimental obstructive jaundice. Therefore, hemorrhage in the presence of jaundice is not due to a deficiency of this component of the plasma.

The fibrinogen content of the plasma is increased in acute obstructive jaundice, probably owing to the irritative effect of the bile on the liver.

The coagulation time remained above normal limits in practically all of the determinations, but it did not parallel the fibrinogen content of the plasma. Corroborating the opinion of Raydin, Riegel and Morrison [25] and Bancroft, Kugelmass and Stanley-Brown,[26] it is concluded that the coagulation time is not a satisfactory index of a hemorrhagic tendency in the presence of jaundice.

The contention of Peters and Van Slyke [8] that a decrease in fibrinogen content of the plasma does not parallel the degree of destruction of the liver is corroborated. It was found that generally an increase in fibrinogen content parallels the extent of damage to the liver.

# ROENTGENOLOGY OF EXPERIMENTAL MESENTERIC VASCULAR OCCLUSION

JAMES S. HIBBARD, M.D.

PAUL C. SWENSON, M.D.

AND

ALFRED G. LEVIN, M.D.

NEW YORK

Mesenteric vascular occlusion still remains one of the most difficult surgical problems. The difficulty in arriving at an early diagnosis undoubtedly accounts for the high mortality, quoted by various writers as being about 70 per cent. The delay in diagnosis is often unavoidable owing to a lack of definite symptoms, even though the damage to the intestinal tract is severe. The same difficulty is experienced in the early clinical diagnosis of simple intestinal obstruction. The effects on the physiology of the bowel of early mesenteric thrombosis or embolism may be compared in some respects with those of simple intestinal obstruction, as well as those of the strangulation type. These conditions result in stasis of the intestinal contents, decrease in the absorption of gas and fluid by the intestinal wall, excretion of fluid into the lumen of the bowel proximal to the affected segment and intestinal hemorrhage and infarction of the involved segment. Although it is an established fact that the roentgen findings of gas and fluid levels in the small intestine have greatly enhanced the diagnosis of simple intestinal obstruction,[1] attention has not been directed to the fact that a similar roentgen picture is produced in mesenteric vascular occlusion.

The object of this paper is to report roentgen studies of experimental occlusion of the mesenteric vessels. The lesions produced in the experimental animals were made to resemble as closely as possible those found in patients.

## PATHOLOGY

In the thirty-six cases reported by Larson,[2] 39 per cent of the vascular occlusions were found to be arterial at autopsy, 44 per cent venous and 17 per cent a combination of the two.

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From the Departments of Surgery and Roentgenology, Presbyterian Hospital, College of Physicians and Surgeons, Columbia University.

1. Swenson, P. C., and Hibbard, J. S.: Roentgenographic Manifestations of Intestinal Obstruction, Arch. Surg. **25**:578 (Sept.) 1932.

2. Larson, L. M.: Mesenteric Vascular Occlusion, Surg., Gynec. & Obst. **53**: 54 (July) 1931.

Klein [3] said that the two types of occlusion are about equally divided. He expressed the belief that arterial occlusion may be caused by either thrombosis or embolism. The etiology of the arterial emboli, which, he stated, include about 2 per cent of cases, must arise in the left side of the heart either from vegetations on the valves or from thrombi in the auricles, as was found in five cases in Larson's series. The arterial thromboses are generally associated with arteriosclerosis, although at times they may be due to pressure of an aortic aneurysm on the artery or to extension of a clot from an aneurysm into the mouth of the artery.

Klein further stated that occlusion of the vein is practically always caused by thrombosis, although some cases are reported in which the etiology is unknown, and others in which only a remote focus of infection exists as a possible cause. The most common cause of venous occlusion is a thrombophlebitis resulting from either acute appendicitis or a pelvic inflammatory condition.

The first effect on the involved segment of intestine of a sudden closure of the superior mesenteric artery, according to most observers, is violent tetanic contractions associated with marked anemia. This condition lasts from two to three hours and is followed by a relaxation and congestion and finally by hemorrhagic infarction. The observations to be reported do not exactly agree with this view. The sequence of events in our experiments was different.

The preliminary contractions were noticed, but numerous subserous hemorrhages varying from 0.25 to 1.5 cm. in diameter resulted within fifteen minutes, and a generalized mild congestion, dilatation and an absence of peristalsis occurred within thirty minutes. This condition was not changed to a great extent at the time the animals were killed, four and six hours later. These phenomena apparently account for the early presence of gas and fluid levels seen in the involved segments on the roentgen film.

Klein stated that all experimenters agree that ligation of the superior mesenteric vein leads constantly to hemorrhagic infarction. He pointed out that in patients the result may be different because it is known that thrombophlebitis generally causes a gradual occlusion. Nevertheless, numerous cases are reported by Larson and others in which an infarcted, congested and soggy segment with dilatation of the proximal intestine was found at operation. These cases would indicate that, although more time is consumed in the process of occlusion, the ultimate outcome is similar to the experimental venous ligations. In the animals of this series, in which the veins to a segment of intestine were ligated, a marked

3. Klein, S.: Embolism and Thrombosis of Mesenteric Artery, Surg., Gynec. & Obst. **33**:385 (Oct.) 1921.

engorgement and a mild contraction immediately occurred, but no relaxation or dilatation followed during the time the abdomen was open. Further, no gas shadows or fluid levels were observed in the involved segment on the roentgen film up to the time the animals were killed, six hours later.

Ligation of both the arteries and the veins of a segment of gut produced the same objective signs that were noted following arterial occlusion, except for the fact that a more marked and rapid congestion and discoloration occurred.

Experimental studies and clinical observations indicate that mesenteric arterial or venous occlusion, severe enough to cause infarction in a segment of intestine, will later cause dilatation of the proximal intestine and result in abdominal distention. These dilated loops of bowel with their fluid levels distributed diffusely over the abdomen will show on the roentgen film.

## EXPERIMENTAL DATA

Three groups of dogs were studied in this series of experiments (table). All of the animals were operated on under ether narcosis and with strictly sterile technic. As soon as gas shadows and fluid levels could be demonstrated on the roentgen films, the abdomen was again opened under ether anesthesia, and the condition of the intestine was observed.

In group A, dog 1, the superior mesenteric artery was ligated just distal to the origin of the inferior pancreaticoduodenal artery. In dog 2, the trunk of the superior mesenteric artery was approached through a retroperitoneal route and ligated about 5 cm. distal to its junction with the aorta. Roentgen films of these two animals disclosed gas shadows, and fluid levels were found on the roentgen film early and simultaneously, i. e., at one and one-half and four hours, respectively. At postmortem examination there were numerous areas of discoloration and a mild dilatation.

Four procedures were done in group B. In dog 1, the portal vein was ligated 6 cm. from its entrance into the liver. In dog 2, the tributaries of the superior mesenteric vein from the jejunum, ileum and cecum were ligated. In dog 3, one half of the jejunum and all of the ileum, and in dog 4, about 12 cm. of the lower ileum were included in the occlusion.

In dogs 1, 2 and 3 of this group no roentgen findings were elicited. When the abdomens were opened six and eight hours later, the entire small intestine and its mesentery were found to be mildly edematous and bluish purple, and the lumen of the intestine was filled with blood. The intestine was not dilated. The negative roentgen findings were probably caused by the fact that the extensive hemorrhage into the lumen of the

bowel displaced the gas. Dog 4 showed no effects from the ligation, since the collateral circulation through the longitudinal branches of the anastomosis apparently was adequate. The animal recovered.

Since the negative results in the first two dogs of the foregoing group were probably due to the filling of the intestinal lumen by blood, two more animals were studied in group B. Our object was to produce a definite

*Results of Experiments*

| | Experimental Animal | Presence of Gas | Presence of Fluid Levels | Vessels Occluded | Condition of Involved Segment |
|---|---|---|---|---|---|
| Group A | | | | | |
| | 1 | 4 hours | 4 hours | Superior mesenteric artery to ileum and jejunum | Slightly dilated; many subserous hemorrhages; gross color: slightly darkened |
| | 2 | 1½ hours | 1½ hours | Superior mesenteric artery to ileum and jejunum | Moderately dilated; many subserous hemorrhages; gross color: slightly darkened |
| Group B | | | | | |
| | 1 | 3½ hours disappeared at 5½ hours | None | Portal vein | Engorged and soggy; bluish red |
| | 2 | 1 hour disappeared at 5 hours | None | Superior mesenteric vein involving jejunum, ileum and proximal colon | Engorged and soggy; bluish red |
| | 3 | None | None | Superior mesenteric vein involving half of jejunum and ileum | Engorged and soggy; contracted; appendix contained gas and fluid; bluish black |
| | 4 | None | None | Superior mesenteric vein involving half of ileum | Animal recovered |
| | 5 | 3 hours | 5 hours | Superior mesenteric vein involving 10 cm. of ileum | Severe hemorrhage; engorged, edematous and contracted in areas |
| | 6 | 3 hours | 5 hours | Superior mesenteric vein involving 10 cm. of ileum | Severe hemorrhage; engorged, edematous and contracted in areas; proximal bowel dilated and contained gas and fluid |
| Group C | | | | | |
| | 1 | 2 hours | 6 hours | Superior mesenteric artery and vein to 40 cm. of ileum | 4 cm. of ileum engorged and soggy; bluish black; proximal gut slightly dilated |
| | 2 | 2 hours | 5 hours | Superior mesenteric artery and vein to 12 cm. of ileum | 4 cm. of ileum engorged and soggy; bluish black; proximal gut slightly dilated |
| | 3 | 2 hours | 4 hours | Superior mesenteric artery and vein to 12 cm. of ileum | 4 cm. of ileum engorged and soggy; bluish black; proximal gut slightly dilated; at 20 hours perforation had occurred; all other cases autopsies at 6 hours |

venous occlusion in a relatively short segment of bowel in the lower ileum. This was accomplished by ligating the mesenteric veins from 10 or 12 cm. of lower ileum and by placing a suture through the mesenteric border of the intestine down through the submucosa, thus obliterating the longitudinal anastomosing branches. This procedure was quite successful in producing a venous occlusion in a small segment of gut. At postmortem examination, the involved segment and its mesentery

Fig. 1.—Film of the abdomen of a dog in the erect position, in which the superior mesenteric artery has been blocked as described in the text. Note the gas shadows and fluid levels, which appeared simultaneously at four hours.

were found to be markedly edematous, hemorrhagic and slightly contracted, and the lumen of the segment and the distal bowel were filled with blood. The proximal intestine was moderately dilated, and gas shadows and fluid levels were found on the roentgen film in three hours and five hours, respectively (fig. 2).

In group C, both the veins and the arteries were occluded in three animals. In dog 1, the mesenteric arteries and veins were ligated to a

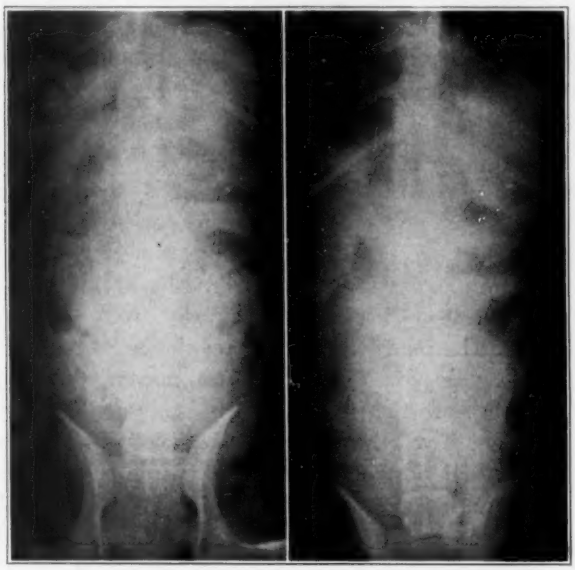

Fig. 2.—Films of the abdomen of a dog in which the tributaries of the superior mesenteric vein, including 12 cm. of the ileum, have been occluded. Note the gas shadows and fluid levels at two and five hours.

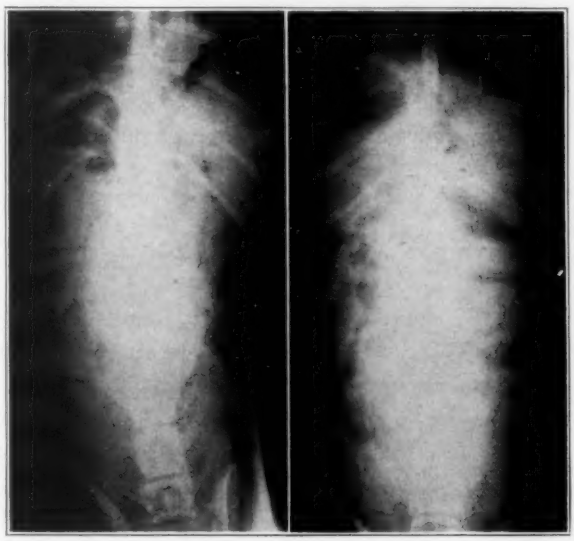

Fig. 3.—Films of the abdomen of a dog in which the superior mesenteric arterial branches and venous tributaries have been occluded through 12 cm. of the ileum. Note the gas shadows at two hours and the fluid levels at four and a half hours.

segment of lower ileum about 40 cm. in length, and in dogs 2 and 3, the occlusions involved about 12 cm. of the lower ileum. The roentgen films disclosed gas shadows in two hours and fluid levels in from four to six hours in all animals (fig. 3).

## COMMENT

This experimental study indicates that it is possible very early to elicit roentgen signs of intestinal obstruction following mesenteric vascular occlusion.

These signs are indistinguishable from those found in mechanical obstruction. Thus, the differential diagnosis from simple mechanical obstruction cannot be made, of course, on the roentgen findings alone, but involves a careful consideration of the accompanying clinical evidence, particularly as to the existence of possible causes of either condition. On the other hand, the important fact remains that the roentgen evidence of intestinal obstruction appears before abdominal distention can be detected and before damage to the involved segment has become too severe. Except in the cases of extensive venous block in which the damage perhaps is too great in any event for surgical relief, the roentgen examination may be a definite aid in reaching a decision to operate.

## SUMMARY

Roentgen examination after experimental occlusion of the mesenteric arteries and veins disclosed gas and fluid levels in dilated loops of small intestine in from two to six hours, which are indistinguishable from those following mechanical intestinal obstruction. However, this evidence should be of aid in early diagnosis and in making an early decision to intervene surgically.

# ESTABLISHMENT OF CIRCULATION IN TUBED SKIN FLAPS

## AN EXPERIMENTAL STUDY

WILLIAM GERMAN, M.D.
NEW HAVEN, CONN.

EDWARD M. FINESILVER, M.D.
NEWARK, N. J.

AND

JOHN STAIGE DAVIS, M.D.
BALTIMORE, MD.

The assurance of the circulation of pedunculated skin flaps [1] is of vast importance in plastic surgery. Often it is possible to form a single pedicled flap and to shift it into its new bed immediately. When this is done one must remember that roughly the length of the flap should not be more than two and a half times the width of the pedicle, unless the flap contains an artery, such as the anterior temporal, in which case it may be as long as the artery will nourish and the pedicle may be very narrow, consisting in fact, if necessary, of only the artery and accompanying veins. Frequently much longer flaps are needed than those that can be conveniently made two and a half times the length of the pedicle, and these must often be obtained from an area in which no definite artery is available.

Flaps that are much more than two and a half times as long as the width of the pedicle may be developed by the delayed transfer method. By delayed transfer we mean that in order to assure its circulation a period of time is allowed to elapse between the raising of the flap and its transference to its its new bed. The best type of flap for the delayed transfer is the doubled pedicled flap, and a very satisfactory double pedicled type is that known as the tubed flap, which was developed during the world war by Gillies of London.

The main advantage of the tubed flap, besides its flexibility, is that it is a doubled pedicled flap the circulation of which is assured by the delay in transfer.

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From the Hunterian Laboratory of Experimental Surgery, Johns Hopkins University, and Department of Surgery, Yale University School of Medicine.

1. A skin flap is made up of the whole thickness of the skin with as much of the subcutaneous tissue as is required. It is usually attached at some portion of its periphery by a pedicle, or pedicles, through which it receives its primary blood supply. A skin graft, on the other hand, is a free transplant whose blood supply is entirely derived from the tissue on which it is transplanted.

The question often arises as to the safest time to sever the pedicles of delayed transfer flaps. In other words, when will the circulation of such flaps be sufficiently developed to allow the division of the first pedicle, so that the circulation from the other will be adequate to nourish the flap without loss of tissue.

It is advised by different authors that from several weeks to as many months should be allowed to elapse before dividing one pedicle and making the transfer, but we have felt that in the majority of instances this long delay, while never disadvantageous as far as circulation is concerned, is actually unnecessary. We have allowed some of these flaps to stay as formed for as long as a year and half before dividing one pedicle and then transferring to its new bed. For the purpose of finding out how soon the circulation of a tubed flap adjusted itself and consequently how soon it was safe to divide the pedicle and transfer the flap, we undertook the following series of experiments in the hope that sufficient information might be obtained to be clinically useful.

## EXPERIMENTAL STUDY

The development of an adequate blood supply in tubed skin flaps is of paramount importance in the utilization of this type of flap. Before the flap can be implanted in a new location, its blood supply from a single pedicle must be sufficient to nourish the entire flap. This necessitates not only an increase in the size or number of the blood vessels, but also a rearrangement of the vessels, corresponding to the long axis of the flap. The present study was undertaken in an attempt to follow, in chronological order, these changes occurring in the vascular bed.

Investigators, in the past, have concerned themselves chiefly with the development of the blood supply of free skin grafts. The development of the blood supply of whole thickness skin grafts has been worked out and the literature reviewed by Davis and Traut.[2] The effect of variations of orientation of skin grafts, in relation to the axis of their original blood supply has been studied by Paterno.[3] Square full thickness grafts were cut and replaced in their original bed. The control grafts were replaced without changing the orientation of their margins and showed 100 per cent survival with reestablishment of circulation after the second day. Grafts rotated 180 degrees with respect to their original orientation survived completely in 80 per cent and partially in 20 per cent of the cases, with reestablishment of circulation

2. Davis, J. S., and Traut, H. F.: Origin and Development of Blood Supply of Whole Thickness Skin Grafts, Ann. Surg. **82**:871, 1925.

3. Paterno, A.: Influenza della variazione di orientamento del lembo sullo attecchimento e sul ripristino dell circulo sanguino nei trapianti libri autoplastici di cute interna, Ann. ital. di chir. **4**:923, 1925.

retarded until after the fourth day. Grafts rotated 90 degrees from their original position survived completely in 66 per cent of the cases, partially in 20 per cent and failed to survive in 14 per cent. Their circulation was retarded until after the fourth day. These results suggest that the establishment of circulation in skin grafts is partially dependent on the orientation of the vessels of the graft in relation to those of the surrounding structures.

## METHODS

In the attempt to study the establishment of a new circulation in tubed flaps, three methods were followed. The first was the determination of the size, number and arrangement of the blood vessels in cleared specimens, removed at intervals of from one to fourteen days following the construction of the tubed flaps. The second method was similar to the first except that an opaque material was injected into the flaps and the studies carried out on roentgenograms of the flaps. The third was a histologic study of the flaps of various ages.

Dogs were used throughout the experiments. The skin of the abdomen was shaved and prepared with iodine and alcohol. With the dogs under ether anesthesia, two double pedicled tubed flaps were outlined, one on either side of the abdominal wall with the long axis of the flap parallel to the long axis of the abdomen. The flaps were 8 to 10 cm. in length and 3 to 3.5 cm. in width, with their bases slightly flared, and were undercut in a manner to include a thin layer of subcutaneous tissue. The edges of the flaps were approximated with interrupted silk sutures, transforming the flaps into tubes with the epithelial surface outside, attached to the abdominal wall at each end in the form of a "valise handle." The skin defect beneath the tubed flap was closed by approximating the opposing skin edges with interrupted silk sutures. Sterile dressings were applied and kept in place for seven days. Usually, healing took place by first intention.

In the first series of experiments, the tubed flaps were separated from the abdominal wall at one end and the animal was given an intravenous injection of from 5 to 10 cc. of 1 per cent solution of toluidine blue, this quantity being sufficient to impart a definite blue color to the skin and mucous membranes. When the blue dye was seen coming from the cut end of the flap, the remaining attachment of the flap to the abdominal wall was cut and the specimen was fixed and cleared, the method [4] of Spalteholz [5] being used. The cleared flaps were then opened along the suture line, spread out flat and mounted in methyl salicylate.

In the second series, the animals were killed, the tubed flaps were separated from the abdominal wall at one end and the injection was made though the aorta. A suspension of barium in gelatin was used as the injection medium.[6] The injection was continued until the barium mixture appeared at the cut end of the flaps. The other pedicle of the flap was then divided, and roentgenograms were taken without opening the flaps.

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4. Fix in formaldehyde; bleach with hydrogen dioxide; wash in water twenty-four hours; dehydrate by passing through alcohols from 50 per cent to absolute; place in benzene (two changes); mount in methyl salicylate, U. S. P., 5 parts and benzyl benzoate 3 parts.

5. Spalteholz, W.: Ueber das Durchsichtigmachen von menschlichen und tierschen Präparaten, ed. 2, Leipzig, S. Hirzel, 1914.

6. Barium sulphate 1,000 Gm., powdered gelatin 300 Gm., distilled water 1,700 cc.

In both the first and second series of experiments, the entrance of the injection material into the flap was through a single pedicle, the upper pedicle being divided on one side and the lower pedicle on the other. This method was selected because the clinical utilization of pedunculated flaps necessitates the development of an adequate blood supply from a single pedicle before the flap can be implanted in a new location. The vessels demonstrated by the injection methods therefore represent the circulation which may be supplied by a single pedicle.

The third series of experiments made use of the flaps of the first series into which toluidine blue was injected. Sections were taken through the central portion of the flaps and stained with hematoxylin and eosin.

Fig. 1.—Typical opened, cleared specimen into which toluidine blue was injected and the flap removed immediately after its construction. Note the blood filled vessels crossing the flap at right angles to its long axis. Only the vessels immediately adjacent to the pedicle showed evidence of containing toluidine blue. Note that there were no vessels running parallel to the long axis of the flap.

## RESULTS

With these three methods of study, the results may be summarized as follows:

Tubed flaps, removed immediately after their preparation showed blood-filled vessels crossing the flaps at right angles to their long axis. Only the vessels immediately adjacent to the pedicle showed evidence of toluidine blue within their lumen. There were no vessels running parallel to the long axis of the flaps.

Flaps removed at the end of one day showed a few vessels, filled with the injection mediums running almost the entire length of the flap. These vessels were more numerous at the region of the base of the flap, but there was a definite tendency for the long axis of the vessels to be parallel to the long axis of the flap.

At the end of four days, vessels containing the injection medium and running parallel to the long axis of the flap, were more marked.

Specimens removed on the seventh day showed what appeared to be a well developed blood supply, with vessels running from one end of the flap to the other.

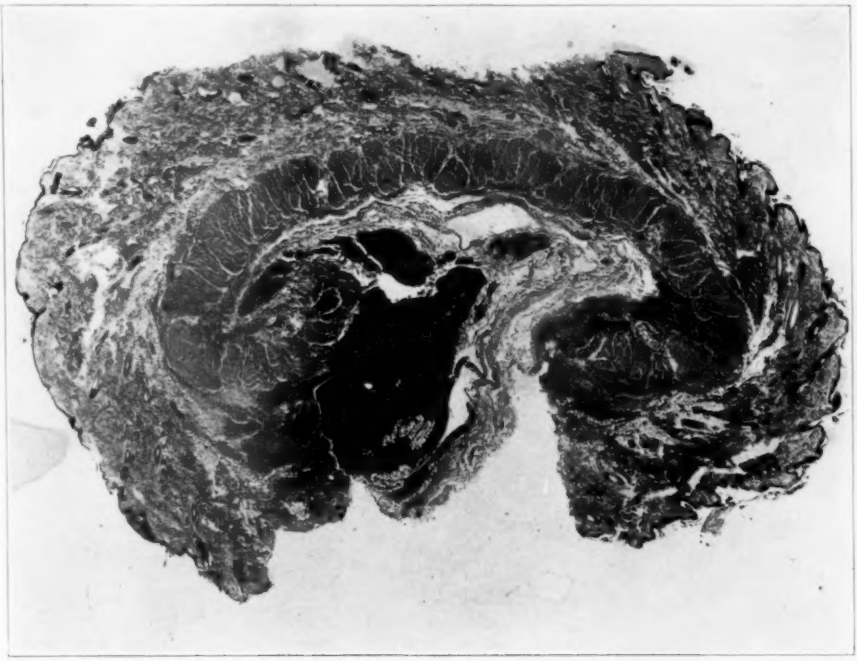

Fig. 2.—Photomicrograph of a section taken through the center of a flap removed immediately after its construction. There are a moderate number of small and medium-sized blood vessels. There is marked hemorrhage in the center of the tubed flap with slight extravasation of blood into the subcutaneous tissue.

From the seventh to the fourteenth day there appeared to be little change in the number, character or size of the vessels.

The microscopic study of sections taken through the central portion of flaps of different ages may be summarized as follows:

On the day of operation there were a moderate number of small and medium-sized blood vessels and marked hemorrhage in the center of the tubed flap with slight extravasation of blood into the subcutaneous tissue.

On the first day a moderate number of small and medium-sized blood vessels were seen with diffuse extravasation of blood throughout the subcutaneous tissue and slight polymorphonuclear leukocytic infiltration.

On the fourth day there were small and medium-sized blood vessels, apparently more in number than on the first day, marked polymorphonuclear leukocytic infiltration in the cutis vera.

On the seventh day there were many small, medium and large blood vessels in the subcutaneous tissue and in the deeper portion of the cutis

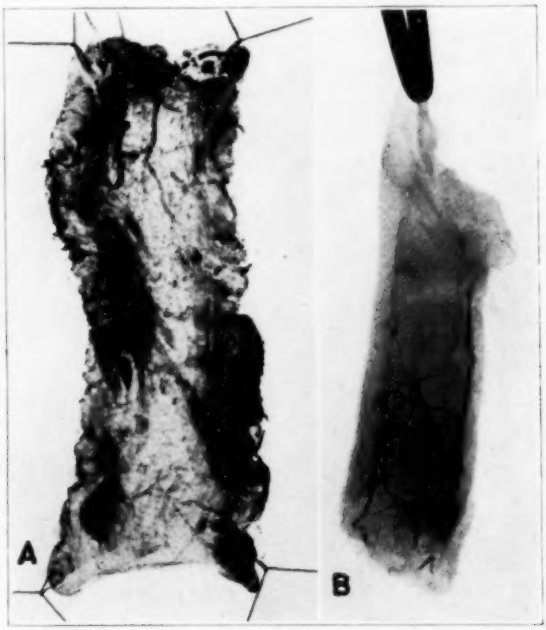


Fig. 3.—*A*, typical opened, cleared specimen into which toluidine blue was injected and the flap removed after twenty-four hours. *B*, roentgenogram of a flap into which an opaque mixture was injected and the flap removed after twenty-four hours. A few vessels filled with injection material can be seen running almost the entire length of the flap. These vessels are more numerous at the region of the base, but there is already a definite tendency for the long axis of the vessels to be parallel to the long axis of the flap.

vera, and early granulation tissue in the cutis vera, containing many capillaries.

On the eleventh day many small, medium and large blood vessels were seen in the subcutaneous tissue and in the cutis vera; there was well developed granulation tissue in the cutis vera.

## SUMMARY OF EXPERIMENTS

Injection experiments of tubed double pedicled skin flaps indicate the establishment of an adequate blood supply from a single pedicle within seven days. Histologic studies of these specimens support this conclusion.

The development of an adequate blood supply appears to be dependent on three factors: (1) an increase in the size of the vessels; (2) an increase in the number of functioning vessels, and (3) a reorientation of the main vascular channels corresponding to the long axis of the flap.

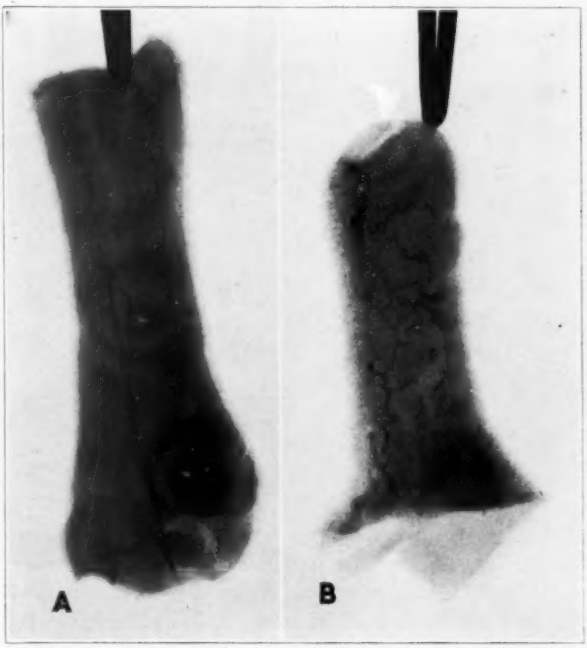


Fig. 4.—Types of roentgenograms of flaps into which an opaque mixture was injected and the flaps removed at the end of four days. The vessels containing the injection medium and running parallel to the long axis of the flap are more marked than in the one day specimens as shown in figure 3.

## CLINICAL APPLICATION

In order to understand the clinical problem with which we are dealing, it may be advantageous to review the anatomy of the blood supply of the human skin.

The anatomy of the cutaneous blood vessels in man has been carefully described and illustrated by Spalteholz.[7] There is a marked

7. Spalteholz, W.: Die Verteilung der Blutgefässe in der Haut, Arch. f. Anat. u. Entwcklngsgesch., 1893, pp. 1-54.

variation in the number and size of the vessels to the skin in different regions of the body. The number is greater to those portions of the skin which are subjected to external pressure, such as the palms of the hands, soles of the feet and the gluteal region.

All branches of the arteries supplying the skin anastomose freely with each other and with neighboring vessels and form a cutaneous arterial network situated in the deepest layer of the cutis. The mesh of this network is smaller in the more vascular regions. From this, arched and branching vessels proceed outward, and anastomosing, form

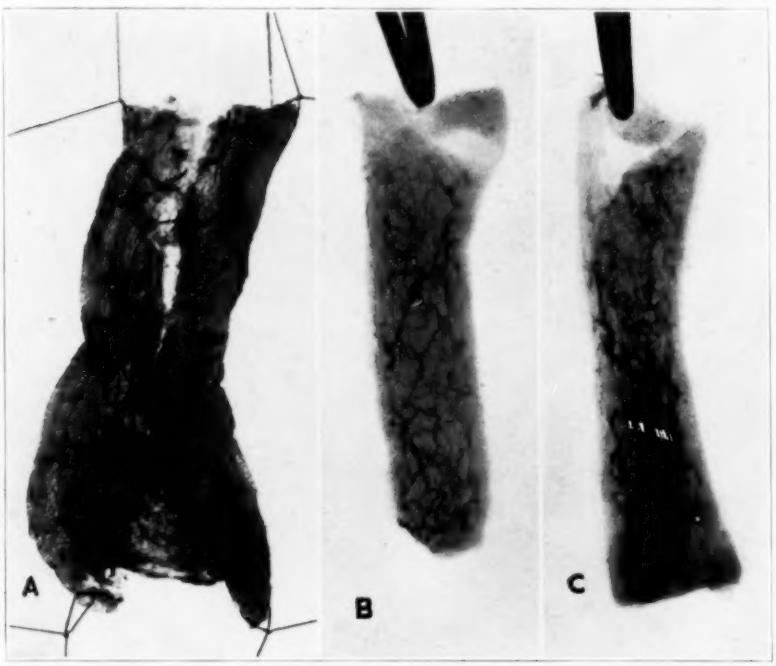


Fig. 5.—*A*, cleared specimen into which toluidine blue was injected and the flap removed at the end of seven days. Compare this with the vessels shown in figures 1 and 3 *A* and note the vessels running the full length of the flap. *B* and *C*, roentgenograms of flaps into which an opaque mixture was injected and removal done at the end of seven days. These specimens show a well developed blood supply with numerous vessels running from one end of the flap to the other. Compare these with figures 3 and 4 and note the marked change in the size and number of the vessels and in the reorientation which has occurred.

a second subpapillary arterial network near the junction of the middle and outer thirds of the cutis.

Numerous small branches arise from the subpapillary network and run as terminal arterioles to the superficial layers of the skin. Most of these turn and course for a short distance parallel to the surface of

the skin, following, in the palm of the hand and the sole of the foot, the direction of the papillary ridges beneath which they run. They send their twigs to the arterial limbs of the capillary loops, lying in the papillae.

The venous blood, returning from the capillary loops in the papillae, passes through several networks. The first lies immediately beneath the bases of the papillae and receives blood from the venous limbs of the capillary loops and from minute collecting venules formed by the union of several such capillaries. Almost immediately beneath this is a second venous network, the two intercommunicating freely by short

Fig. 6.—Photomicrograph of a section taken through the center of a flap removed at the end of seven days. There are many small, medium and large blood vessels in the subcutaneous tissue and in the deeper portion of the cutis vera. There is also early granulation tissue in the cutis vera containing many capillaries. A comparison of this section with that in figure 2 is interesting as it shows the marked increase of blood vessels both in size and number which have developed in seven days.

venules; these two networks are often termed the subpapillary venous plexus. The blood flows deeper by numerous tributaries to a third and fourth venous network, the former lying immediately deep to the subpapillary arterial plexus, the latter at the level of the cutaneous plexus of arteries, where cutis and subcutis join.

The general arrangement of the vessels is illustrated in the diagram (fig. 9), modified from that originally published by Spalteholz.

Thomas Lewis,[8] in his monograph on the blood vessels of the human skin, utilized a somewhat less involved terminology in distinguishing the various vessels, classifying them as strong arterioles, minute vessels and deep veins.

The classification used by Lewis is much simpler than that prepared by Spalteholz. If detail is desired in descriptions the classification of Spalteholz is to be preferred, but for ordinary use that of Lewis is sufficient.

The results of the experimental work have been so significant, that although we have not had the opportunity of making injections into

Fig. 7.—Photomicrograph of a section taken through the center of a flap removed at the end of eleven days. There are many small, medium and large blood vessels in the subcutaneous tissue and in the cutis vera. There is also well developed granulation tissue in the cutis vera. There is not much difference in the development of the blood vessels shown in this section and that shown in the seven day specimen in figure 6.

flaps on human beings, we feel justified in surmising from clinical observations along the same line that much the same process takes place as in the animal experiments, and that in a tubed flap the normal vessels of the human skin also increase in size and number and that the

8. Lewis, T.: The Blood Vessels of the Human Skin and Their Responses, London, Shaw & Sons, 1927.

main vascular channels are reoriented to correspond to the long axis of the flap.

The information obtained from the animal experiments seemed worthy of a careful clinical tryout. This was checked at first on patients as follows. Tubed flaps which had been prepared for transplantation to definite defects were used. We started with the division of the pedicle on the fourteenth day and gradually reduced the time until now in suitable cases we sometimes divide the pedicle on the tenth day. However, we usually prefer to divide the selected pedicle piecemeal, that is, a third or half way through on the tenth and the

Fig. 8.—Typical roentgenogram of a flap into which an opaque mixture was injected and the flap removed at the end of fourteen days. There is little change to be noted in the vessels on comparison of the fourteen and the seven day specimens, either in number, character or size.

remainder on the eleventh or twelfth days, depending on whether the separation is done in halves or thirds, and have adopted this as a routine procedure in dealing with ordinary tubed flaps. Frequently there is definite arterial bleeding from the end of the tube when the pedicle is divided. This usually comes from near the central portion of the flap, but sometimes is well to one side or the other.

From the experimental data we might be justified in starting this division as early as the seventh or eighth day, but as yet we have not

chanced the loss of a portion of the flap by trying this out clinically and think it safer not to begin the division of the first pedicle until the tenth day (fig. 10).

If there is doubt in the mind of the operator as to the vitality of the tube in any particular case, it is, of course, advisable to delay the division for full two weeks, or as much longer as conditions require. From the standpoint of the comfort of the patient, there is usually no particular hurry in dividing the first pedicle. On the other hand, when to divide the base pedicle, when the flap comes from a distant part, say from the arm to the face, is a much more important matter to the patient, on account of the enforced irksomeness of the position. We

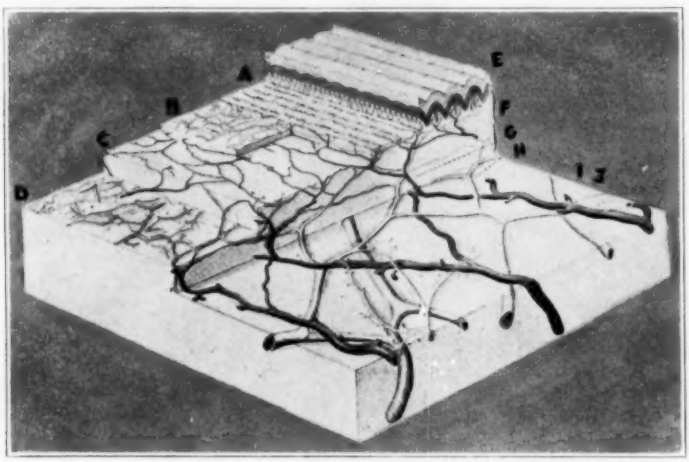


Fig. 9.—Diagram showing the arrangement of the human cutaneous blood vessels, Spalteholz' classification being used (Lewis). *A* and *B* indicate the subpapillary venous plexus (*A*, the first venous plexus and terminal arterioles and *B*, the second venous plexus); *C*, the subpapillary arteriolar plexus; *D*, the third venous plexus; *E*, the epidermis; *F*, the cutis; *G*, the arched arterioles; *H*, the fourth venous plexus; *I*, the sweat gland layer; *J*, the cutaneous arterial plexus.

have found that when the tube has been opened out for one-third its length or more and has been sutured in close contact with its new bed, that, all other conditions being favorable, we can begin to divide the pedicle as early as the eighth or ninth day and have the arm down on the tenth or eleventh day rather than wait two weeks as we had previously done. In these cases there is often profuse bleeding from both ends of the divided pedicle showing a good circulation originating in this period of time from the new base, as well as from the original source of blood supply.

Fig. 10.—The early division of pedicles and transference of a tubed flap from the arm to cheek. *A*, a tubed flap 13 cm. long formed on the inner side of the arm. This flap was planned in width, length and position to fill a defect to be made by the excision of a contracted scar of the cheek and lip. Note the complete formation of the tube, the type of pedicles and that the skin has been sutured beneath the tube. The lower pedicle was divided in stages beginning on the tenth day, and the division was completed on the eleventh day at which time the flap was opened for about half its length and was transferred and sutured, after raising the arm, into the defect on the cheek made by the excision of the contracted scar tissue and for which it had been prepared. *B* and *C*, the base pedicle on the arm was gradually divided beginning on the ninth day. Note the partial division in *B*. The division was completed on the tenth day. There was free bleeding from the stump attached to the cheek. This stump was opened and utilized. No portion of the flap was lost by the early division of either pedicle. *D*, the final result of the transfer of the tubed flap. Note the smooth normal looking skin which fits into its new environment quite naturally.

SUMMARY

The clinical application of the information obtained in this experimental study has been successfully tried out on tubed flaps during the last three years. It has also been of value in determining the time of division of the pedicles in those long pedicled flaps which are raised and without being tubed are immediately sutured back into the bed from which they came until ready for transfer.

The longer the tubed flap is allowed to remain intact, within certain limits, the more stable the blood supply becomes, but from our observations, both clinical and experimental, we are convinced that the establishment of circulation in tubed skin flaps occurs considerably earlier than was previously thought possible and consequently that it is safe to divide the pedicles sooner.

# A PATH OF INFECTION IN PERINEPHRITIS

HARRY C. ROLNICK, M.D.
CHICAGO

Last year, before the Chicago Urological Society, Dr. Burstein and I reviewed a series of fifty-five cases of perinephritic abscess.[1] Thirty-two were metastatic in origin. The metastatic abscesses are of particular interest because they are usually diagnosed only when the condition has become well developed. They are, in the vast majority of cases, primarily cortical abscesses of the kidney,[2] thus accounting for the difficulty in their diagnosis. The abscess at first does not communicate with the renal pelvis, so that the urinary and pyelographic findings are negative until some weeks later, when the abscess has extended and communicates with the pelvis. The outer capsule undergoes inflammatory reaction and encapsulates the abscess, and thus here also evidence does not usually present itself until the abscess has spread into the perinephric tissue, when it is possible to make the diagnosis by the presence of a tumor, the finding of pus by aspiration or roentgenologic evidence.

The various modes of invasion in perinephritis are pictured in the accompanying diagram (fig. 1). One of the paths of extension of infection—that along the periureteral sheath, of which very little mention has been made in the literature—is here shown.

Since that report, I have operated in twelve cases of perinephritic abscess, one of which was bilateral. Two of these cases are of particular interest in that they indicate the path of infection as the sheath of the ureter. Other postoperative and postmortem observations are also of interest, for they show quite definitely the ureteral sheath as the pathway of infection from the pelvis upward and from the kidney down. These various observations prompted the experimental roentgenologic observations on postmortem specimens of kidneys, ureters and bladder, which will be reported. The various clinical observations will be briefly mentioned first.

## REPORT OF CASES

CASE 1.—In a woman, five days after a normal labor, a chill developed, followed by a fever which persisted for weeks and which was septic. There were no pelvic or urologic findings. After six weeks some tenderness and rigidity in the right

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Read before the Chicago Urological Society, April 23, 1931.

1. Rolnick and Burstein: Perinephritic Abscess: A Review of a Series of Cases, J. Urol. **25**:507 (May) 1931.

2. Hunt, V. C.: Perinephritic Abscess, J. A. M. A. **83**:2070 (Dec. 27) 1924.

loin prompted incision of this region. A large perinephritic abscess, which had extended in sacculations from the pelvis up to the kidney, was drained. Six weeks later, a left perinephritic abscess was drained. This abscess also extended along the posterior part of the peritoneum from the base of the bladder up to the kidney.

CASE 2.—In a man aged 55, who gave a history and rectal findings of a chronic prostatovesiculitis, a septic temperature with some tenderness in the right lumbar region developed. Cystoscopic, urinary and roentgen findings were negative. A diagnosis of perinephritic abscess was made two weeks later by puncture and aspiration. At operation a large abscess, extending up to the kidney but lying in the dead space below it, was drained. Exposure of the ureter showed marked thickening and irregularity throughout its entire course from the bladder to the kidney.

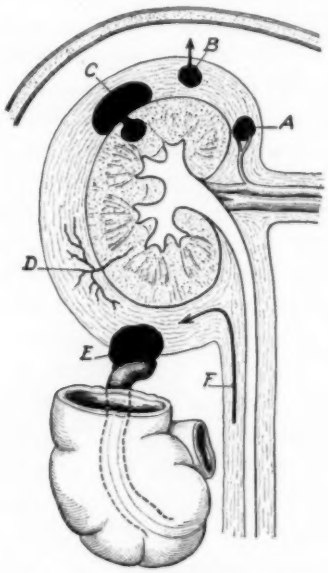


Fig. 1.—Diagram to show sources of perinephritic abscess. *A*, hematogenous form, face of infection elsewhere in body; *B*, extension of perinephritic abscess to subphrenic space; *C*, extension of infection from cortical abscess of kidney to fat around it; *D*, same as *C*, but by way of lymphatics; *E*, retrocecal appendiceal abscess extending to perinephric fat, and *F*, extension of infection from prostate, etc., along periureteral sheath. (From Eisendrath and Rolnick: Urology, Philadelphia, J. B. Lippincott Company, 1930, p. 690.)

In the first case, the abscess may have developed and extended upward by continuity along the posterior peritoneum from the base of the bladder to the kidney. It may also have extended along the sheath of the ureter.

In the second case, the evidence at hand, the previous prostatovesiculitis, with negative urinary findings, and the irregularity, thickening and beading of the ureter indicate extension along the sheath of the ureter. The abscess did not involve the perinephric tissue, for it

had most likely broken through the ureteral sheath at one or more points before extending to the kidney.

CASE 3.—Ten days following a low ureterotomy for stone, the patient required exposure of the kidney of that side because of pain, tenderness and rigidity over the lumbar region, together with chills and fever. An abscess was found which was entirely subcapsular and had no renal involvement.

Here also the extension of the infection, undoubtedly from the site of the ureterotomy wound, was either along the lymphatics of the wall of the ureter or more likely along the sheath of the ureter.

CASE 4.—Two days following a difficult nephrectomy in a case in which a small portion of the pelvis was left because it was bound down toward the median line very close to the vena cava, funiculitis of the spermatic cord of that side with some tenderness developed. This gradually subsided and cleared up completely when the patient left the hospital eighteen days following the operation.

CASE 5.—A nephropexy for kink of the ureter, in which the ureter was freed from adhesions, was followed within thirty-six hours by a rather marked crepitus of air emphysema in the spermatic cord of the same side high up in the scrotum. There was no scrotal emphysema. The patient made an uneventful convalescence, the emphysema clearing up within six days.

Cases 4 and 5 indicate rather clearly the path of the funiculitis and the air emphysema of the spermatic cord as the sheath of the ureter and by extension at the junction of the ureteral sheath with that of the seminal vesicle along the sheath of the vas to the external inguinal ring. A few years ago, I demonstrated the possibility of infection along the sheath of the vas,[3] and also presented clinical evidence of the same. Abscess and funiculitis usually present themselves in the groin at Bogros's space,[4] a loose band of connective tissue separating the pelvic from the scrotal vas.

CASE 6.—At operation for a transcapsular rupture of the kidney, a fairly marked hematoma was present; blood had also extravasated along the posterior peritoneum downward for some distance along the sheath of the ureter.

CASE 7.—Autopsy in a man who had a marked pelvic infection disclosed a calculus in the cavity of a prostatectomy wound of a year before. This had eroded through the prostatic capsule. The inflammatory involvement extended downward along the sheath of the vas up to the scrotal portion and also upward along the sheath of the ureter and posterior peritoneum up to the perirenal tissues.

These various observations of extension of infection from the pelvis upward and from the kidney downward, with no associated urinary findings, as shown in the first five cases, indicate the path of infection as

3. Rolnick, H. C.: Infections Along the Sheath of the Vas Deferens, J. Urol. **14**:371 (Oct.) 1925.

4. Belfield, W. T., and Rolnick, H. C.: Roentgenography and Therapy with Iodized Oils, J. A. M. A. **86**:1831 (June 12) 1926.

along the outer wall of the ureter or its sheath. The rapid extension downward of pus and air to the spermatic cord and of blood along the sheath of the ureter is strong evidence of extension of the process along the sheath of the ureter and by continuity along the sheath of the vas.

Considerable experimental work has been done on ascending infection of the kidney. Eisendrath and Schultz [5] showed that infection may extend upward along the anastomotic chain of lymphatics in the wall of

Fig. 2.—Postmortem specimen of bladder, ureter and kidney; the peritoneum is still attached to the ureter. The periureteral sheath is shown with injection of contrast medium throughout most of its length.

the bladder and ureter, and that ascending infection can develop in this manner secondarily from infection of the prostate and seminal vesicle.

Belfield,[6] in his classic paper on "Pus Tubes in the Male," described the intimate relation of the ureter, vesicle and vas as the broad ligament

5. Eisendrath and Schultz: J. M. Research **35**:295 (Jan.) 1917.

6. Belfield, W. T.: Pus Tubes in the Male, J. A. M. A. **53**:2141 (Dec. 25) 1909.

in the male and showed the close proximity of the fascia and sheath of the seminal vesicle with that of the ureter.

Von Lichtenberg [7] discussed pathologic involvement of the upper urinary tract secondary to adnexal disease in the male and showed varying degrees of hydronephrosis and renal infection resulting therefrom, some cases even requiring nephrectomy. These all resulted from compression of the lower part of the ureter by the seminal vesicle and stric-

Fig. 3.—Postmortem specimen of bladder, ureter and kidneys; contrast fluid is shown injected into both ureteral sheaths extending from the base of the bladder up almost to the kidney.

ture of the ureter, owing to extension of infection to the ureter from the prostate and seminal vesicles.

Considerable emphasis has been given of late to the importance of adnexal disease in the male in pathologic involvement of the upper urinary tract. Von Lichtenberg [7] spoke of the junction of the urinary and genital tracts in the male at the point where the vas crosses the

7. von Lichtenberg: J. Urol. **24**:1 (July) 1930.

ureter and the seminal vesicle comes in contact with the ureter as a bad corner. At this point, there is a common nerve, blood and lymph supply. The ureteral sheath communicates here with that of the seminal vesicle and also with the loose fascia at the base of the bladder in both males and females.

The sheath of the ureter covers the ureter along its entire course, extending upward from the base of the bladder, enveloping the renal

Fig. 4.—Various specimens showing the injection of the periureteral sheaths with contrast fluid at various points along their course.

pelvis and infiltrating and covering the fatty and true renal capsule. Within this sheath the ureter has considerable of its blood, lymph and nerve supply. In performing a ureterotomy for stone, it is best to leave the ureter attached to the peritoneum. Traction on the ureter and separation from the peritoneum may result in separating it from its sheath. Slough of the ureter and persistent fistulas may result from depriving it of its blood, lymph and nerve supply. It is, therefore, evident that the ureteral sheath is an important structure, and that it also permits possible extension of infection.

The periureteral sheath is also considered in Eisendrath and Rolnick's[8] "Urology" as a path of extension of infection to the perirenal tissue from the parametria, prostate, seminal vesicles and bladder.

## EXPERIMENTAL DATA

The experiments for the purpose of determining the accuracy of the various clinical observations were made as follows:

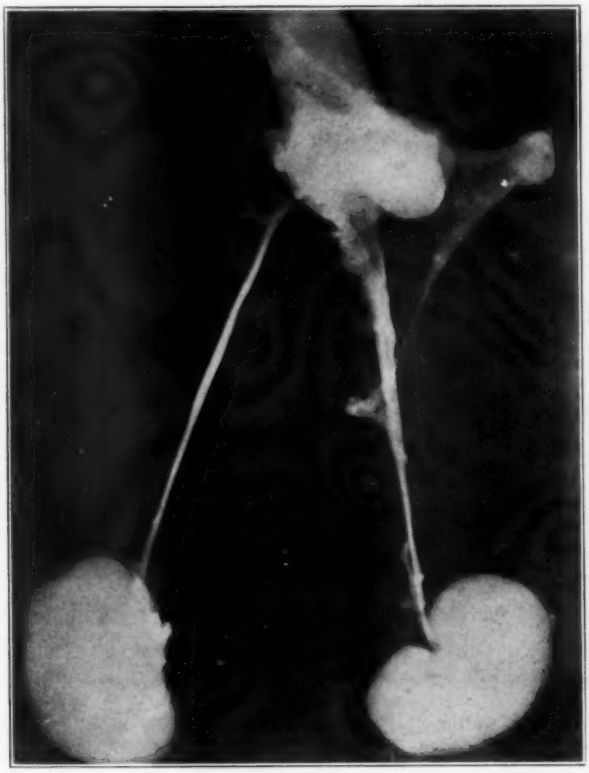

Fig. 5.—Specimen showing the injection of the periureteral sheath of each side with contrast fluid practically its entire length.

Fresh postmortem specimens of both kidneys, ureters and bladder were employed. The specimens were from both males and females, children and adults; in all, thirty were obtained over a period of a few months. In the male the adnexae were also attached.

A contrast fluid of from 25 to 30 per cent sodium bromide solution was injected into the ureteral sheath, and the specimen was then roentgenographed. Injections were begun either in the fascia at the base of the bladder near the ureter or within

8. Eisendrath, D. N., and Rolnick, H. C.: Urology, Philadelphia, J. B. Lippincott Company, 1930, p. 689.

the sheath of the seminal vesicle. In others, injection was made directly into the ureteral sheath, beginning at the juxta vesicular portion of the ureter and extending upward. In a few specimens the injections within the sheath were begun at the renal pelvis and carried downward. In practically all instances, the contrast fluid could be forced very readily upward or downward along the sheath of the ureter. In the female, infiltration of the loose tissues at the base of the bladder permitted the forcing up and milking upward of the contrast medium in the ureteral sheath. The accompanying illustrations (figs. 2, 3, 4, 5 and 6) show the ureteral sheath into which contrast fluid was injected in the various ways mentioned.

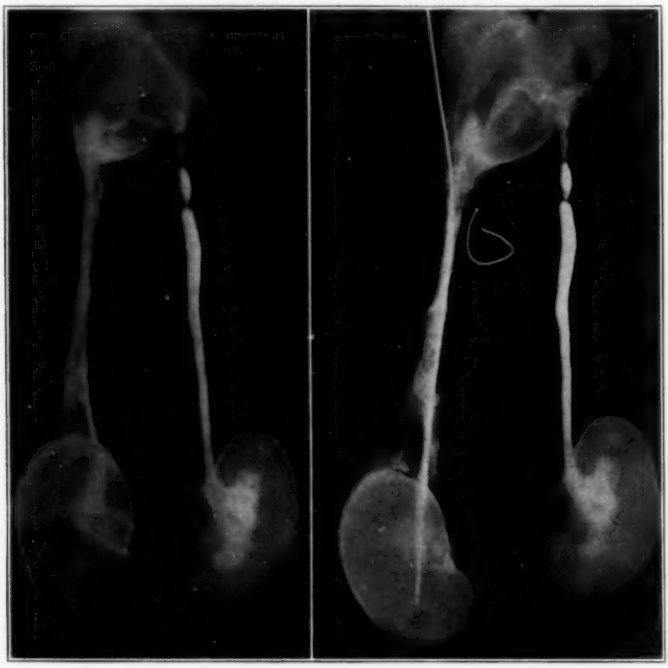

Fig. 6.—In each of these specimens, pyelograms and ureterograms have been made of one side to show the contrast with the other side in which injection into the ureteral sheath has been made. On the left hand side injection has been made into the ureteral sheath, from the base of the bladder upward. Air has been injected into the lumen of the ureter. On the right hand side, a ureteral catheter has been inserted into the lumen of the ureter, and injection made into the ureteral sheath from the bladder upward.

## COMMENT

This, I believe, is the first time that the possibility of extension of infection along the sheath of the ureter has been demonstrated roentgenographically. These clinical and experimental observations should be of particular interest to gynecologists as well as to urologists. There are many clinical observations by both gynecologists and urologists of adnexal and pelvic infection causing infection of the upper urinary tract.

The demonstration of extension of infection along the sheath of the ureter is of decided clinical importance.

Bands and adhesions about the ureter and renal pelvis, periureteritis, peripyelitis and perinephritis, acute and chronic and of varying degrees of severity, including perinephritic abscess, may result from extension of infection along the sheath of the ureter secondary to pelvic infection in both male and female.

Dr. Jaffé, pathologist at Cook County Hospital, and his associates procured the specimens used in these experiments.

Dr. Kaplan, radiologist at Mount Sinai Hospital, did the roentgenographic work on the specimens.

# RESECTION OF SENSORY NERVES OF PERINEUM IN CERTAIN IRRITATIVE CONDITIONS OF THE EXTERNAL GENITALIA

JAMES R. LEARMONTH, F.R.C.S. (Ed.)
HAMILTON MONTGOMERY, M.D.
AND
VIRGIL S. COUNSELLER, M.D.
ROCHESTER, MINN.

The purpose of this paper is to form some estimate of the efficacy of neurectomy of sensory nerves in the treatment of certain irritative lesions of the female external genitalia. The intolerable itching which may be associated with such conditions as kraurosis, leukoplakic vulvitis and pruritus of the vulva with or without lichenification is often particularly resistant to local medication, whether this consists in the application of drugs or in exposure of the region to roentgen or actinic rays. This distressing symptom not only leads to excoriation of the parts, but also reduces the physical and moral stamina of the patient by depriving her of sleep. Two surgical procedures are available for the treatment of these conditions: vulvectomy and section of the sensory nerves to the parts. The choice of operation may be simplified by the occasional appearance of malignant lesions in the course of one of these diseases, a matter that has been recently dealt with by one of us;[1] in such cases either simple or radical vulvectomy, according to the degree of malignancy, is obviously the correct treatment. In cases in which there is not any suspicion of malignant degeneration, section of the sensory nerves of the area avoids the element of mutilation inseparable from vulvectomy. At first sight it would appear that neurectomy is merely symptomatic treatment; however, we have evidence that this operation may have a healing effect on the cutaneous lesions. This evidence, with a description of the histologic appearance of the skin before and after operation, will be presented in a subsequent paper.

## THE NERVES OF THE EXTERNAL GENITALIA

The pudic nerve (fig. 1) is derived chiefly from the third and fourth sacral segments of the spinal cord, and also receives a small contribution

From the Section on Neurologic Surgery, the Section on Dermatology and Syphilology and the Division of Surgery, the Mayo Clinic.

1. Counseller, V. S.: Leukoplakic Vulvitis or Kraurosis Vulvae; Its Relation to Carcinoma and Its Surgical Treatment, Minnesota Med. **14**:312 (April) 1931.

from the second sacral segment. It enters the ischiorectal fossa around the lower border of the small sacrosciatic ligament, and runs on the inner aspect of the obturator internus muscle in a fascial tunnel known as Alcock's canal. At first it has the pudic artery and veins on its outer side, but soon takes up a position superficial to these vessels. Soon after its appearance in the fossa it gives off its inferior hemorrhoidal branches, which cross the space to supply the posterior part of the

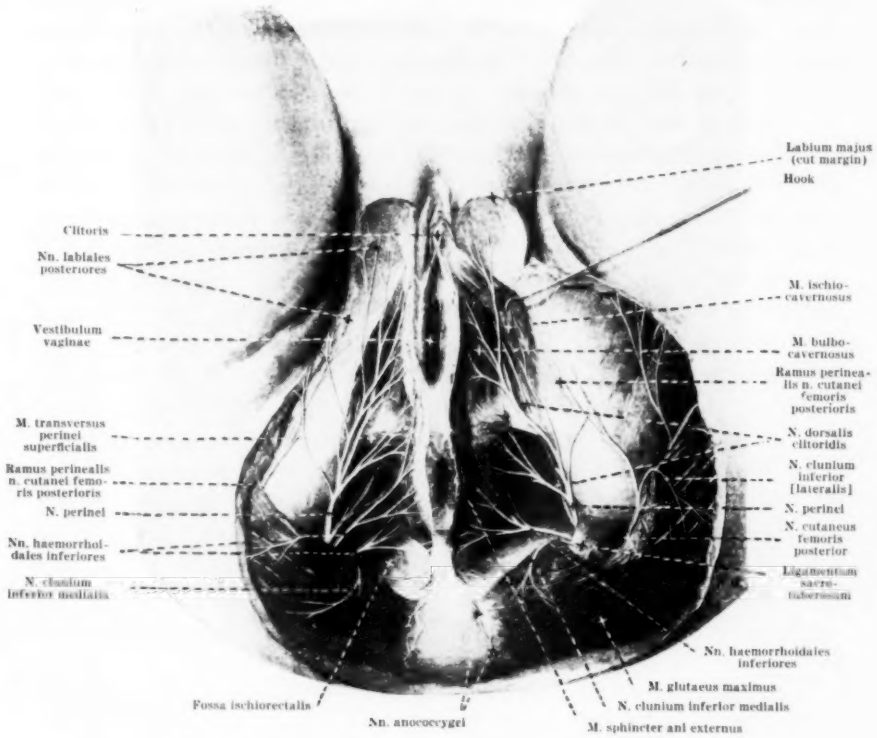


Fig. 1.—The anatomy of the pudic nerve (Spalteholz).

external anal sphincter and the skin overlying this; not uncommonly, however, these branches arise directly from the sacral plexus and enter the fossa separately. The trunk itself courses forward and becomes more superficial; it ends by dividing into the perineal nerve and the dorsal nerve of the clitoris. Sometimes the trunk divides into these in the posterior part of Alcock's canal; sometimes its final division is delayed until it reaches the superficial transverse muscle; usually the separation into its terminal branches takes place about the middle of

Alcock's canal. Wherever they are formed, the perineal nerve lies superficial to the pudic vessels, and the dorsal nerve of the clitoris deep to them.

The perineal nerve almost at once divides into two branches: superficial and deep. The superficial perineal nerve is purely sensory, and passes forward to divide into the external and internal labial nerves, which may be traced at least as far as the middle of the labia majora; the external nerve usually goes superficial to the transversus perinei muscle, the internal nerve through or deep to that muscle. The external labial nerve anastomoses with the pudendal branch of the small sciatic nerve. The first offshoot of the deep perineal nerve is a branch for the anterior part of the sphincter ani externus. When the pudic nerve divides about the middle of Alcock's canal, this anal branch passes transversely to its destination; on the other hand, when the final division of the pudic nerve is delayed until it reaches the posterior border of the superficial transverse muscle, the anal branch curves backward and somewhat inward to reach the sphincter. The uncertainty of the course pursued by the anal nerve makes it necessary for the surgeon to identify and avoid it during resection of the sensory nerves of the area. The deep perineal nerve then leaves the fossa by passing deep to the superficial transverse muscle and between the two layers of the triangular ligament; it is expended chiefly in the supply of the muscles in the anterior part of the perineum: the superficial transverse muscle, the posterior part of the constrictor urethrae,[2] the ischiocavernosus and the sphincter vaginae; it also sends branches to the bulb of the vestibule.

The dorsal nerve of the clitoris passes between the two layers of the triangular ligament, in company with the pudic artery; in this part of its course it gives motor fibers to the anterior part of the constrictor urethrae. Close to the symphysis it pierces the triangular ligament and ends in the supply of the clitoris.

The small sciatic nerve, which is derived from the first, second and third sacral nerves, also contributes to the sensory innervation of the external genitalia. One of its descending branches, the pudendal branch, runs mesially and forward, and courses toward the vulva about 2 cm. lateral to the ramus of the ischium. Finally, it pierces the deep fascia, and after anastomosing with the external labial nerve, it is distributed to the posterior half of the labium majus, and to the adjacent part of the skin of the perineum.

The anterior third of the labium majus derives its sensory supply from the terminal branches of the ilio-inguinal nerve and the genital

2. Including that part of this muscle sometimes separately described as the transversus perinei profundus.

branch of the genitocrural nerve. The ilio-inguinal nerve is derived from the first, and the genitocrural from the first and second lumbar segments of the spinal cord.

The cutaneous areas subserved by each of the main sensory nerves are shown in figure 2, which has been modified from Tavel.[3] On account of the rich anastomosis between their terminal twigs, the area supplied by each nerve is not sharply demarcated, and as a corollary the division of any one of them does not lead to complete paralysis of sensation in the territory attributed to it. This is especially the case with the labial nerves, the fine terminal branches of which often appear to overlap the field of the ilio-inguinal and genitocrural nerves. However, sensation

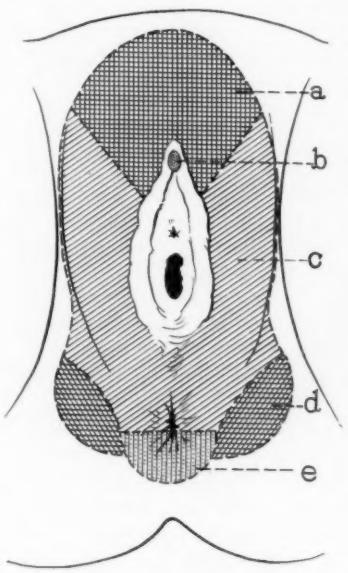


Fig. 2.—The cutaneous distribution of the nerves of the perineum in the female (modified from Tavel): *a*, ilio-inguinal and genitocrural nerves; *b*, dorsal nerve of clitoris; *c*, superficial perineal nerve; *d*, pudendal branch of small sciatic nerve, and *e*, inferior hemorrhoidal nerve.

in the posterior two thirds of the labia majora may be greatly blunted by division of the superficial perineal nerves and the pudendal branches of the small sciatic nerves; the clitoris may be added to this area by division of its dorsal nerves.

From an analysis of the sensory innervation of the perineum, it will be apparent that in order to allay irritation about its hinder part, the surgeon should aim at dividing the superficial branches of the perineal

3. Tavel, E.: La résection du nerf honteux interne dans le vaginisme et le prurit de la vulve, Rev. de chir. **25**:145, 1902.

nerves, the pudendal branches of the small sciatic nerves and, if necessary, the dorsal nerves of the clitoris. The muscular branches of the deep perineal nerves to the anterior part of the sphincter ani must be carefully preserved; the nerves to the posterior part of the sphincter ani are not likely to be displayed during the operation.

## TECHNIC OF OPERATION

For seventy years sporadic reports of operations on the pudic nerves have appeared in surgical and gynecologic literature. Most of these reports attribute the first operation to Sir James Y. Simpson [4] of Edinburgh, but give a reference to one of his papers which does not allude to neurectomy. The correct reference [4] contains a description of the procedure, under the heading "Hyperaesthesia and Neuralgia of the Vulva," and gives priority in its use to Dr. Burns of Glasgow. This description is quoted to show the first step in the evolution of the operation. It may be added that the temporary nature of the results obtained by the original method were obviously due to regeneration of the nerves.

"There is one other morbid condition of the female genital organs, regarding which you must allow me to say a word or two during the few minutes we have still at our disposal. It is observed chiefly in married women who come to you complaining that contact with a certain point in the sides of the vaginal orifice, or vulva, causes them such acute suffering that they are totally unable to endure any attempt at marital intercourse. This pain seems to be due to a state of hyperaesthesia of the pudic nerve, and was first described by Dr. Burns, of Glasgow, who, in his Principles of Midwifery, after describing the anatomical distribution and relations of the nerve, goes on to say that it 'is often preternaturally sensible, so as to cause great pain in coitu, as well as at other times. It may be exposed, by cutting through the skin and fascia, at the side of the labium and perineum; beginning on a line with the front of the vaginal orifice, and carrying the incision back for two inches. The nerve being blended with cellular substance is not easily seen in such an operation; but it may be divided by turning the blade of the knife, and cutting through the vagina to its inner coat, but not injuring that. It may be more easily divided by cutting from the vagina. Slitting, merely, the orifice of the vagina will not do; we must carry the incision fully half an inch up from the orifice, and also divide the mucous membrane freely in a lateral direction.' I formerly knew one or two patients who had consulted Dr. Burns in regard to this affection, and in whom the pudic nerve had been divided in the manner he describes, either by himself or by his son; yet in these patients the painful sensation returned, though sometimes not in the same place, but in the track of some other nerve. I believe, with Dr. Burns, that the best palliative treatment for such cases is division of the affected nerve; but, instead of laying it bare, I have usually cut it through subcutaneously, by means of an ordinary tenotomy knife. It is a surgical measure far more simple in its character. Occasionally there is greater supersensitiveness and neuralgia of the vulva and vaginal orifice, without there existing any local lesion whatever capable of accounting for it. The pain is not then usually limited to any one single point. Such cases require the usual constitutional treatment of neuralgia, as iron, manganese, arsenic, etc., sometimes in long-continued

4. Simpson, J. Y.: Clinical Lectures on the Diseases of Women: Lecture 10. On Caruncles of the Urethra—Neuromata of the Vulva—Hyperaesthesia and Neuralgia of the Vulva, M. Times & Gaz. **39**:333 (April 2) 1859.

courses. You have to use general anti-neuralgia tonic medicines and measures; and locally all forms of sedatives and anodyne applications."

Alternative methods for resecting the nerves of the perineum have been described by Rochet [5] and Tavel, and recently by Wertheimer and Michon.[6] It is possible to approach the resection by either of two plans: by finding the trunk of the pudic nerve, and then tracing it peripherally to the desired branches, or by finding certain peripheral branches and tracing them proximally to the terminal branches of the trunk. In our experience the second method has proved satisfactory (figs. 3 and 4).

The patient is placed in an exaggerated lithotomy position, and the parts are prepared. The steps of the operation are the same on both sides. The length of the incision varies from 7.5 to 10 cm., depending on the obesity of the subject. It is placed parallel to and about 3 cm. from the rami of the ischium and pubis, about

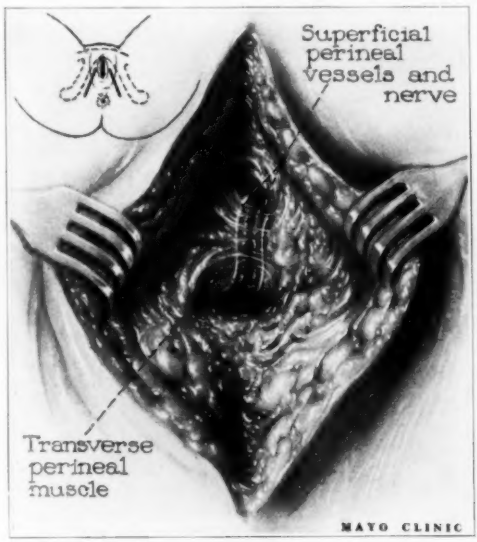


Fig. 3.—Division of nerves of vulva, first stage. Inset, the incisions.

five sixths of it being anterior to the anus. An incision so placed rarely gives rise to subsequent discomfort in walking or sitting. The incision is deepened by blunt dissection until the posterior border of the superficial transverse muscle is reached. The superficial perineal packet of vessels and nerves is then isolated as it turns forward around the muscle. It is not unusual for this packet to contain only the inner of the two labial nerves; the outer labial nerve should then be sought as it turns around the border of the muscle. We have not found it of any advantage to attempt to preserve the small arteries and veins in the packet; it is divided between two clamps. The outer nerves in the grasp of the distal clamp are then traced distally, in an attempt to find their anastomosis with the pudendal branch

5. Rochet, V.: Traitement chirurgical des prurits périnéaux, anaux et vulvaires, Lyon méd. **100**:570, 1903.

6. Wertheimer, P., and Michon, L.: La névrotomie du nerf honteux interne: indications, technique, résultats, J. de chir. **31**:497 (April) 1928.

of the small sciatic nerve; if the latter is reached it is divided and its distal portion is twisted out. If it is not reached, the labial nerves and vessels are ligated as far forward as possible, or twisted out, and the tissues thus isolated are removed. The nerves in the grasp of the proximal clamp are then traced proximally until the perineal branch of the pudic nerve is reached. The twigs of this nerve that run to the anal region are carefully safeguarded; if it is necessary to denervate the skin of this area, each terminal twig must be tweaked; only the twigs that depress the skin when tweaked are to be resected. The branches between the perineal nerve and the proximal clamp are removed, after ligation of any vessels. In this way a segment of the labial nerves from 5 to 8 cm. long may be resected, and a segment from 2 to 3 cm. long of the sensory branches of the perineal nerve to the skin around the anus.

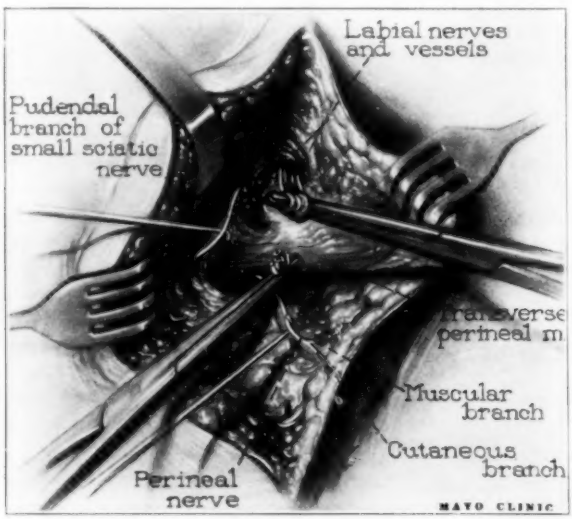


Fig. 4.—Division of nerves of vulva, second stage.

If the dorsal nerve of the clitoris is to be resected, it may be found deep to the pudic artery, by following the perineal nerve (or bundle of nerves) toward the pudic trunk on the surface of the obturator internus muscle. Alternatively, if the division of the pudic nerve has taken place in the posterior part of its course, the dorsal nerve of the clitoris may be sought directly in Alcock's canal.

If it has been impracticable to isolate the pudendal branch of the small sciatic nerve in front, an attempt may be made to find the branch as it approaches the perineum. It runs parallel to and about 2 cm. to the outer side of the ramus of the ischium, and may be sought in this situation after retraction of the outer lip of the wound.

The deep layers of the wound are then approximated by a few points of catgut, and the incision in the skin is closed. We have not found it necessary to employ drainage. A similar procedure is then carried out on the opposite side. The postoperative treatment does not differ from that of any other operation on the perineum.

PREVIOUSLY RECORDED OPERATIONS

Two cases have been recorded by Rochet:[5]

A woman, aged 48, had pruritus for more than ten years; even the vagina and the urethra itched. Apparently the trunk of the pudic nerve was divided on both sides; the pudic vessels were preserved. The itching was relieved for at least three years.

A man, aged 50, had pruritus of the anus and scrotum for two years. The superficial branches of the perineal nerve, its branches to the skin around the anterior part of the anus and the pudendal branch of the small sciatic nerve were divided on both sides. The patient was completely relieved, and the cure persisted for at least eight months.

One case has been recorded by Murard:[7]

A woman, aged 54, underwent subtotal hysterectomy in 1922, under spinal anesthesia. A day or two after the operation she began to have symptoms of two distinct types: a feeling of weight in the perineum, with a sensation of fulness in the bladder leading to frequency, and pruritus of the vulva. Seven years after the original operation, the pudic nerves were divided on both sides. Five weeks later the pruritus had disappeared, and the parts appeared healthy. The presence of the perineal scars gave rise to a little inconvenience in walking Murard was of the opinion that an injury to the roots of the cauda equina during the administration of the spinal anesthetic was the exciting factor in the case, but in the discussion which followed its presentation, Basset stated that an analysis of a large series of cases in which spinal anesthesia was used did not lend support to this view.

One case has been recorded by Mauclaire:[8]

A woman, aged 34, two months after a pelvic operation, began to suffer from intense vulvovaginal pruritus, much pelvic pain and some vaginismus. At a second laparotomy, adhesions were separated and the remaining ovary was partially resected. The pruritus became worse. Eight months after the original operation, the right dorsal nerve of the clitoris and the left perineal nerve were resected. The patient was relieved of her symptoms, except that some vaginismus persisted.

One case has been recorded by Albertin:[9]

A woman had suffered for eight years from pain in the bladder and vulvovaginal pruritus. On the right side the resection was limited to the perineal nerve, and on the left side the pudic nerve and artery were resected. The pruritus was relieved for the forty-five days the patient remained under observation. It is noteworthy that, after the neurectomy, the passage of a catheter could still be felt.

One case has been recorded by Tavel:[3]

A woman, aged 48, had suffered for a number of years from pruritus of the vulva, and an extreme degree of vaginismus. On the right side the perineal nerve

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7. Murard, Jean: Troubles vaso-moteurs et hyperesthésiques consécutifs à une rachianesthésie. Traitement par névrotomie des honteux internes, Bull. et mém. Soc. nat. d. chir. **55**:1153 (Nov. 6) 1929.

8. Mauclaire, P.: A propos du prurit vulvaire traité par le névrotomie bilatérale des nerfs honteux internes, Bull. et mém. Soc. nat. d. chir. **55**:1210 (Nov. 30) 1929.

9. Albertin: Résection des nerfs honteux internes, Lyon méd. **100**:572, 1903

was avulsed, its anal branch being preserved; on the left side the perineal nerve was avulsed in its entirety. Three months later the patient was entirely relieved, but had a little trouble in retaining a liquid stool.

One case has been recorded by Bérard and Wertheimer:[10]

A woman, aged 52, had had intense pruritus of the vulva for fifteen months. This resisted local treatment and periarterial sympathectomy of both internal iliac arteries. The perineal branch of the pudic nerve was divided on both sides. The result was excellent; not only was there symptomatic relief, but the cutaneous lesions were much improved. Two years later the patient had a mild recurrence of itching, which yielded to rest in bed.

### CASES OBSERVED AT THE MAYO CLINIC

CASE 1.—A woman, aged 45, came to the clinic on Oct. 31, 1930, complaining of itching of the vulva which had begun in 1928, after panhysterectomy. The patient had not obtained satisfactory relief from local applications. About the clitoris, and between the fourchet and the anus, were several rough and elevated whitish patches. The vulva was markedly atrophied. A diagnosis was made of kraurosis of the vulva and beginning leukokeratosis near the fourchet.

On November 13, a specimen of skin was removed immediately posterior to the fourchet. Thereafter both branches of the superficial perineal nerve were divided, on both sides, at the posterior border of the superficial transverse muscle; the pudendal branch of the small sciatic nerve was also divided on both sides. On December 1, the wounds had healed, after some drainage from the wound on the left. The patient expressed herself as completely relieved. Two days later a dermatologist assessed the decrease in leukokeratosis at 75 per cent. On Jan. 9, 1931, the patient's family physician wrote that the vascularity of the tissues was much increased, and that the itching had disappeared entirely. An area 1 cm. in diameter to the left of the clitoris was still white and caused discomfort at times. In December, 1931, the patient was well pleased with the result of the operation.

The tissue removed showed the histopathologic picture of leukoplakia.

CASE 2.—A woman, aged 49, came to the clinic on Nov. 28, 1930, complaining of intense itching of the vulva of four years' duration. This had resisted treatment by local measures. On the inner aspects of the labia majora the skin was thick and white, and showed numerous excoriations at their upper angle. The labia minora were absent. There was relatively little atrophy of the skin, the latter being for the most part thick, white and soggy. A diagnosis was made of pruritus of the vulva, which some authorities would possibly term kraurosis in the hypertrophic stage.

On December 4, the perineal branches of the pudic nerve were divided on both sides. The pudendal branch of the right small sciatic nerve alone was divided; that of the left nerve was not identified. A portion of skin was removed for examination. On December 19, itching was still felt at night. A small area of soggy skin was still present around the clitoris. On Feb. 16, 1931, some itching was still present on the right side. On Jan. 13, 1932, the patient reported that she had had little relief from the operation, and that the presence of the perineal scars somewhat interfered with walking.

Sections of the skin removed at the operation showed the histopathologic picture of kraurosis of the vulva in its hypertrophic stage.

10. Bérard, L., and Wertheimer, P.: Kraurosis vulvae. Névrotomie des nerfs honteux internes. Guérison, Lyon chir. **23**:524, 1926.

CASE 3.—A woman, aged 61, came to the clinic on Feb. 28, 1931, complaining of itching about the anus and vulva, of nine years' duration. This had been treated elsewhere by injections of alcohol about the anus and external genitalia, but without success. The vulva was edematous and swollen. The mucous membrane was blanched, and there was a small area of necrosis and sloughing on the inner aspect of one labium majus. The skin on the inner aspects of both thighs was mildly irritated. The perianal skin showed similar but less severe lesions. A diagnosis was made of kraurosis of the vulva and anus, and leukoplakic vulvitis with lichenification and abrasions.

On March 4, the perineal nerve on the right side was divided, including a branch to the skin around the anus, and a similar resection was performed on the left side. The pudendal branches of the small sciatic nerves were not divided. A small piece of skin was removed for examination. On March 25, the vulva was less gray and more pinkish. There was not any evidence of scratching or leukoplakia. On June 1, scratch marks and erythema were both absent. The vulva had the usual light pink tint seen in older life. The patient was completely relieved of the itching.

The skin from the vulva showed the microscopic features of both kraurosis and leukoplakia.

CASE 4.—A woman, aged 49, came to the clinic on June 29, 1931, complaining of intense itching about the vulva, of thirteen years' duration; at times this had been so intense that the parts had been scratched until they were raw. Local treatment had not been of any avail. She had had some trouble in controlling the rectal sphincter. A diagnosis was made of pruritus of the vulva, with slight kraurosis, and mild prolapse of the rectum.

On July 8, the neurovascular packet containing the right superficial perineal nerves and vessels was divided. On the left side the vessels were dissected from the nerves, and only the latter were resected. During the dissection the right pudic artery was wounded and had to be tied, and the trunk of the right pudic nerve was also divided. A small piece of skin was removed for histologic study.

On July 20, the patient was relieved of the itching. She still had some trouble in controlling the rectal sphincter. On August 25, she reported that she had complete relief from itching; the rectal trouble persisted. On Feb. 5, 1932, she reported that the operation had been "a perfect success."

The skin from the vulva showed the histopathologic picture of neurodermatitis.

CASE 5.—A woman, aged 55, came to the clinic on July 9, 1931, complaining of itching of the vulva of thirteen years' duration. Local treatment had not resulted in improvement. Around the vulva and anus there were pigmentation, excoriation and definite atrophy involving the inner aspects of the thighs as well as the vulvar folds. Patches of superficial ulceration were present in these areas. A diagnosis was made of kraurosis of the vulva.

On July 24, an ulcerated area near the clitoris was removed for histologic examination. Thereafter the superficial perineal branches of the pudic nerve and the pudendal branch of the small sciatic nerve were resected on both sides. On August 8, the patient was completely relieved of itching. On Jan. 16, 1932, she reported that her condition was greatly improved; a little itching about the urethra was still present, at night only.

The portion of skin removed showed the histopathologic picture of leukoplakia.

CASE 6.—A woman, aged 40, came to the clinic on Aug. 27, 1931, complaining of itching of the vulva of ten years' duration. The first lesions had appeared on the inner aspect of the right thigh. After various local measures had been tried,

a series of applications of radium was made (elsewhere) over the vulva. The labia majora were edematous and red. Their skin was atrophic and contained numerous telangiectatic vessels. Above the clitoris were several moderately deep crusted ulcerated lesions, involving both labia. A diagnosis was made of pruritus and actinodermatitis of the vulva.

On September 1, the superficial perineal nerves and the pudendal branch of the small sciatic nerve were divided on both sides. On September 15, the itching had disappeared. In spite of their unfavorable situation both wounds had healed by primary union. On Jan. 12, 1932, the patient reported that she was in excellent condition and had no itching, and that all the ulcerated areas had remained healed. A biopsy was not performed in this case.

CASE 7.—A woman, aged 55, came to the clinic on Aug. 11, 1931, complaining of itching of the vulva of four years' duration. A diagnosis was made of kraurosis, involving the labia minora and clitoris.

On August 19, a specimen was removed for histologic examination; the superficial perineal nerves and the pudendal branch of the small sciatic nerve were resected on both sides. On September 2, the only itching area remaining was a small patch near the clitoris, where skin had been removed. On September 17, the patient reported that there had been some discharge from both wounds. On November 2, a further report stated that the itching had almost completely disappeared. In January, 1931, the patient reported that she had periods of itching about three times in each twenty-four hours.

The skin removed at operation showed the histopathologic picture of kraurosis of the vulva.

## FUNCTION AFTER OPERATION

*The Depth of Sensory Paralysis.*—It has been pointed out that the sensory supply of the female genitalia is not demarcated in strict zones, so that an accurate assessment of the sensory changes which result from neurectomy is difficult. We have found that the area of blunting of sensation corresponds fairly closely to the territory assigned in figure 2 to the perineal nerves, although an attempt has not been made to separate their territory from that of the pudendal branches of the small sciatic nerves. In one of our successful cases tactile sensibility was not absent, although it was somewhat depressed, the principal change observed being analgesia, graded —2 to —3 on a basis of 4. Although single, this is an interesting physiologic observation, for elsewhere in the body the division of a sensory nerve usually produces more extensive anesthesia than analgesia. As a corollary it is of interest that the irritation which is called itching was suppressed in an analgesic area, although touch could still be felt; the orthodox view appears to be that itching is felt by way of tactile fibers. We were unable to detect any such dissociation of anesthesia in our remaining cases.

*The Control of the External Sphincter of the Anus.*—The posterior fibers of the external anal sphincter receive their motor nerves through the inferior hemorrhoidal branches, the anterior fibers from the perineal branches. The preservation of the inferior hemorrhoidal nerves is scarcely a matter for concern, because they do not hamper the operator

and indeed may not appear in the field. More care is necessary to preserve the muscular branches to the anus that are derived from the perineal nerve; they were divided on one side in Tavel's case, without any gross loss of rectal control. Division of the trunks of the pudic nerves distal to their inferior hemorrhoidal branches would leave the motor nerves to the posterior half of the sphincter intact, and in these circumstances it is likely that the combined action of the smooth internal sphincter and the posterior half of the external sphincter would assure control, except of liquid stools and after the administration of purgatives.

*The Control of the Constrictor Urethrae.*—In women the striated muscle fibers surrounding the urethra lack the purposive arrangement

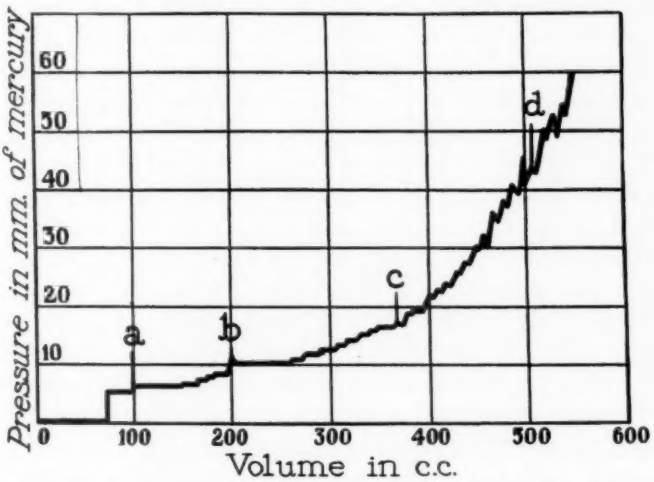


Fig. 5.—Normal cystometrogram, after division of the right pudic nerve and the left superficial perineal nerve: *a*, first appreciation of cold; *b*, first desire to void; *c*, first feeling of pain, and *d*, severe pain.

found in men. For the most part, they are set irregularly among the smooth muscle fibers that surround the wall of the tube. A part of this striated system is sometimes separately described as the transversus perinei profundus, and has assigned to it a function comparable to that of the external sphincter in men. This part of the sheet of striated muscle that closes the pelvic outlet in its anterior half can scarcely function as a true sphincter, because its fibers pass only behind the urethra, and form a sling for it rather than a circular controlling muscle.

The sheet of striated muscle fibers around the urethra receives motor nerves from the deep branch of the perineal nerve and from the dorsal nerve of the clitoris, the territory of the latter nerve being anterior to

that of the former; although its arrangement in the female is not mechanically adapted to function as a sphincter, the question of control of the bladder after operations on the pudic nerves is naturally of great importance. When the resection is limited to the purely sensory superficial perineal branches this question does not arise, but when it is desirable to divide the deep perineal branch and the dorsal nerve of the clitoris the surgeon must be able to assure his patient that the operation will not be followed by vesical incontinence. This sequel has not followed neurectomy, either in our hands or in those of others; evidently, in women, the smooth sphincter is sufficient to provide, not only for retention of the urine, but for its periodic evacuation. If any branches of the pudic nerves played an essential part in vesical control, incontinence of urine ought to have followed operation in our case 4, in Rochet's case 1, in Murard's case, in Mauclaire's case and in Albertin's

*Neurectomy of Perineal Nerves*

| Observer | Patient Observed; Time | Result |
|---|---|---|
| Rochet | 3 years | Completely relieved |
| Bérard and Wertheimer | 2 years | Slight temporary recurrence after two years |
| Learmonth | 14 months | Almost completely relieved |
| Learmonth | 13 months | Little, if any, relief |
| Rochet | 8 months | Completely relieved |
| Learmonth | 7 months | Completely relieved |
| Learmonth | 6 months | Almost completely relieved |
| Learmonth | 4 months | Completely relieved |
| Learmonth | 4 months | Almost completely relieved |
| Learmonth | 3 months | Completely relieved |
| Tavel | 3 months | Completely relieved |
| Albertin | 7 weeks | Completely relieved |
| Murard | 5 weeks | Completely relieved |
| Mauclaire | Not stated | Relieved of pruritus; some vaginismus persisted |

case. In our case 4, a normal cystometrogram was obtained after the operation (fig. 5).

## CONCLUSIONS FROM RESULTS OF OPERATIONS

The results of the fourteen operations reviewed in this paper are best tabulated according to the period during which the patient remained under observation (table).

Experience has shown that the immediate effect of operation is to banish the pruritus. This desirable result has been absent in only one case (our case 2). We have not been able to explain this failure, as a result either of difficulty in performing the operation, or of any peculiarity of the vulvar lesion; it must be accepted as a failure. Granted that immediate relief is the rule, it is obvious that the permanence of relief depends on the possibility of regeneration in the severed nerves; therefore, only the first four cases in the table are of value in assessing the late results of operation. In case 1 the result might well be called permanent. In case 2 the possibility arises that the recurrence after the elapse of

two years was due to the restoration of additional sensibility to the skin, although the temporary nature of the recurrence is against this view. In case 3, the interval since operation is scarcely long enough to permit labeling the result permanent. In case 4 the result was a failure from the first. In the remaining ten cases, assessment of the immediate relief alone can be made; this was satisfactory in all.

It follows that every care must be taken at operation to resect or twist out sufficient lengths of the desired nerves to reduce the likelihood of restoration of their continuity. In their course the superficial perineal nerves undergo a sharp change in direction, and moreover their origin from the perineal nerve is on a substantially deeper plane than is their cutaneous distribution. It appears to us that the restoration of any considerable degree of innervation is unlikely in the territory of the labial nerves. It is otherwise for the nerves supplying the skin anterior to the anus. Their direction and plane correspond to those of the parent nerve, and it is not possible to resect more than a short segment of them; to guard against regeneration, the parent branches may be doubled back and tied in this position.

The operation appears to be well borne. Two patients in the complete series complained that the perineal scars interfered with walking; in one of these (our case 2) the operation had been totally ineffective, and in the other (Murard's case) the surgeon was unable to detect any alteration in the gait of the patient. We have indicated that a carefully performed operation does not prejudice the function either of the bladder or of the rectum.

To sum up, we feel that neurectomy may well be offered to patients suffering from irritative conditions of the vulva, except those of two types: When there is any suspicion of malignant change, vulvectomy is the only procedure to be considered, and when the patient is so fat that identification of the various nerves would be tedious and perhaps uncertain, vulvectomy provides the quickest solution of the problem.

## SUMMARY

The anatomy of the sensory nerves of the perineum is described.

The operation of neurectomy of the sensory nerves of the perineum is described.

Fourteen cases are considered in which this operation has been performed for irritative lesions of the vulva.

The number of cases and the length of time they have been observed do not permit an opinion as to the permanence of the relief afforded by the operation. Nevertheless, it is recommended as the primary treatment in such cases, unless there is any suspicion of malignant change, or the patient is so obese that neurectomy would be difficult and uncertain.

# ACUTE ABDOMINAL SYMPTOMS IN ARACHNIDISM

CHARLES BRUCE MORTON, M.D.
UNIVERSITY, VA.

Several cases of arachnidism, a clinical syndrome due to the bite of the "black widow" spider, the Latrodectus mactans, seen recently at the University of Virginia Hospital presented abdominal symptoms of great severity. If the true condition had not been recognized, exploration of the abdomen for an acute surgical abdominal emergency might have been readily undertaken. The ease with which this confusion might occur—witness the reports of several such patients subjected to operation elsewhere—and the apparent lack of consideration given the subject in the surgical literature suggested this résumé of arachnidism with particular reference to its abdominal manifestations.

The first case af arachnidism that came to my attention, case 1 of the series reported herewith, was not seen until the symptoms had commenced to subside, and the diagnosis was not made until several weeks after the patient had been discharged from the hospital. The diagnosis was made at that time through a conversation with a surgeon [1] in a neighboring city. He described the case of a man who had been sent to him a short time previously for operative treatment of a suspected perforation in a peptic ulcer. He felt that the symptoms and signs were not entirely typical and asked a medical consultant to see the case with him. The internist suspected arachnidism and elicited the fact that the patient had been bitten by a spider a few hours previously. Had this diagnosis not been made, the patient would have been subjected to an exploratory laparotomy for the suspected perforation of a peptic ulcer.

After hearing the symptoms and signs of this case described, I reviewed the history of case 1 and found them to be almost identical. With this background, it was not unduly difficult to make the correct diagnosis in the subsequent cases of the series reported herewith. In fact, case 2 created so much interest that the intern staff made the diagnoses in the later cases and admitted the last two patients, not to the surgical wards as candidates for operation, but to the medical wards for teaching purposes.

## REPORT OF CASES

CASE 1.—C. L. S., a white man, aged 29, was admitted to a private room in the University of Virginia Hospital at 7 p. m. on Oct. 10, 1930. He complained of

1. Bigger, I. A.: Personal communication.

rather severe pain in the abdomen. He had awakened at 5 a. m. with a slight tingling pain in the left popliteal space. He had not noticed any swelling or redness at the site. The pain had gradually radiated up the left leg to the scrotum and the left groin. In a short time he had been seized with excruciatingly severe, cramplike pain throughout the abdomen and toward the region of the left kidney. He had consulted his family physician, who had suspected renal colic and had administered morphine by hypodermic injection. He had been slightly relieved, but the cramplike pains had persisted, with exacerbations at intervals of three or four minutes, throughout the day. Because of the persistence of the pain, the patient had consulted another physician, who sent him to the hospital and asked me to see him in consultation.

At that time a careful review of the history revealed nothing additional of positive value. There was no knowledge of any recent blow, injury or insect bite. There had been no urinary symptoms, no nausea or vomiting, and the bowels had moved normally that morning.

Examination revealed a well nourished young man in obvious pain, restless and somewhat anxious looking. His temperature was 99.6 F. by mouth; the pulse rate was 52 per minute, and his respiratory rate, 36 per minute. His respirations were rather shallow and somewhat labored. The blood pressure was elevated. There was no evidence of redness, swelling or heat and no pain or tenderness in the popliteal space, the left thigh, the groin or the scrotum. The abdomen was slightly tender throughout, and there was marked rigidity of the abdominal muscles, which felt boardlike. There was a little tenderness in the region of the left kidney. There seemed to be no abnormality of the muscle or tendon reflexes. Repeated urinalyses failed to demonstrate white or red blood cells, and there was no sugar or albumin in the urine. The leukocytes numbered 14,000 per cubic millimeter of blood.

No definite diagnosis was made. The perforation of a peptic ulcer was considered, but there was something indefinable about the consistency of the abdomen, which taken in conjunction with the absence of nausea and vomiting, the slow pulse rate, and the peculiar onset of the symptoms did not seem consistent with this diagnosis. Because of the pain in the left leg and the region of the left kidney, the tentative diagnosis of renal colic was made and continued careful observation advised.

The next morning the patient's pain had subsided to a considerable degree, and the tenderness and rigidity of his abdomen were scarcely perceptible. His temperature was normal, and the leukocytes numbered 12,500. Later that day he felt well enough to go home, and was allowed to do so.

For a few days he was followed by the medical consultant as an office patient, and repeated urinalyses still failed to reveal any abnormal findings. Five days later a small, slightly indurated area was palpable in the left popliteal space. It soon disappeared, however. The patient's history was filed under "no diagnosis." As previously mentioned, the diagnosis of arachnidism was not realized and made until several weeks later, after hearing the history of a case from a surgeon of another city.

CASE 2.—T. D., a white man, aged 21, was admitted to the surgical ward service of the University of Virginia Hospital on Sept. 20, 1931, at 3:30 p. m. He complained of severe pain in the abdomen. He had arisen that morning feeling perfectly well, had eaten fried ham, bread and coffee for breakfast at about 9 a. m., and then had gone to an outhouse toilet and had a normal bowel movement. While there he had not been conscious of anything like the bite or sting of an insect. Half an hour later he had started out of his house but had been seized

suddenly with such a severe pain in the lower part of his abdomen on the right side and extending to the right groin that he had gone back into the house to lie down. The pain had increased so much that he had called his family physician, who administered morphine hypodermically. The pain had persisted, and the physician had sent the patient to the hospital because he suspected some acute intra-abdominal disease that necessitated surgical treatment. There had been nausea but no vomiting. There had been no urinary symptoms or chills.

Immediately after the patient entered the hospital, examination revealed a well nourished, healthy looking young man apparently suffering considerable pain. His temperature was 99 F. by mouth; his pulse good and its rate 104 per minute, and his respirations were 24 per minute. Physical examination gave essentially negative results, except for the abdomen, which was slightly tender throughout and quite rigid. The rigidity was boardlike in character throughout, though a little more marked on the right side than the left. All muscle and tendon reflexes were normal. The leukocytes numbered 10,200, and examination of the urine revealed no abnormality. Four hours later the patient's temperature was 100 F. by mouth, and the leukocytes numbered 13,500. The pulse was of good quality, and its rate was only 70 per minute. In spite of the failure to elicit the history of a spider bite, I made the diagnosis of arachnidism and advised symptomatic treatment rather than the exploratory laparotomy which had been previously considered.

The patient's subsequent course proved the wisdom of this decision, for his symptoms gradually subsided and the next day he was sufficiently well and comfortable to go home. At that time his leukocytes and temperature were normal. Some days later his local physician reported that the man was entirely well and apparently none the worse for his experience.

Case 3.—N. E. D., a white man, aged 55, the father of T. D. (case 2), was admitted to the surgical ward service of the University of Virginia Hospital on Sept. 29, 1931, at 9:00 p. m. He complained of pain in his abdomen, legs and back of about twelve hours' duration. At 7:00 a. m. he had gone to the same outhouse toilet as that visited a week previously by T. D. (case 2), and while there felt a sharp, needle-like sting on the right side of his scrotum. He had not seen what stung him and had not given the incident any further consideration. About two hours later, however, he had felt pains in both knees which had radiated up the thighs and localized in the abdomen and back. The abdominal pain had been quite severe and accompanied by nausea and vomiting. He had been most comfortable when lying down with the thighs flexed on his abdomen. During the day the pain had increased in severity, and he had called a physician to see him. The physician, who was not the same one who had attended his son, sent him to the hospital for surgical consideration.

Examination revealed a well nourished, elderly-looking man apparently suffering considerably. His temperature was 101 F. by mouth, the pulse rate 80 and the respiratory rate 24 per minute. His systolic blood pressure was 140 and the diastolic 75 mm. of mercury. The only abnormal physical findings were a small erythematous spot about 1 cm. in diameter on the right side of the scrotum and slight tenderness throughout the abdomen with very marked rigidity of the abdominal muscles. His leukocytes numbered 16,200, but urinalysis revealed no abnormal findings. The intern house officer who admitted the patient to the hospital made the diagnosis of "arachnidism."

The patient improved rapidly, though he suffered from a rather severe and persistent headache. All his symptoms disappeared so that he was able to go home thirty-six hours after the time of his admission to the hospital.

CASE 4.—W. H., a Negro, aged 31, was admitted to the surgical ward service of the University of Virginia Hospital on Oct. 12, 1931. He complained of severe pain in his abdomen of about twelve hours' duration. His symptoms, signs and physical and laboratory findings did not differ in any essential respect from those recounted in the first three cases, except that he had seen and felt a spider bite him. During the night he had visited an outhouse toilet, and just taken his seat when he felt a sharp sting on the foreskin of the right side of the penis. He had a flashlight with him, and when he illuminated the painful area he saw "a black spider with long legs and red spots on his body" clinging to the skin. The abdominal pain had commenced an hour or two after the spider bite had occurred.

CASE 5.—E. B., a white youth, aged 18, was admitted to the medical ward service of the University of Virginia Hospital on Nov. 18, 1931. He complained of severe abdominal pain of seven hours' duration. He had been awakened at 5 a. m. by the pain and had no knowledge of a previous insect bite. All the features of this case were practically identical with those of the previous four cases so they will not be detailed further.

CASE 6.—J. L. G., a white man, aged 35, was admitted to the medical ward service of the University of Virginia Hospital on Nov. 25, 1931. He complained of extremely severe cramplike pain in the abdomen of ten hours' duration. About an hour before the onset of the pain he had felt a sting of some sort on the right wrist while loading rocks on a wagon from a rock pile. The symptoms and abnormal findings characteristic of the previous five cases were found in this instance too, so that the details will not be repeated.

## COMMENT

The most striking feature of all the cases was the relative ease with which the correct diagnosis could be made, even without the history of the bite of a spider, if the condition were borne in mind, but likewise the ease with which the mistaken diagnosis of an acute surgical intra-abdominal disease such as perforated peptic ulcer might be made if one were not familiar with the symptoms and signs of arachnidism.

The outstanding symptom in each case was the severe and usually cramplike abdominal pain, while the most prominent physical abnormality was the extreme boardlike rigidity of the abdominal musculature. Regarding the pain in the abdomen, it is important to note that in most of the cases there was an associated pain or ache in the muscles of the thighs or the back. Concerning the rigidity of the abdominal muscles, it is important to note that the tenderness was much less marked than that usually accompanying the rigid abdomen of a perforated peptic ulcer or appendix.

Arachnidism is characterized by the acute onset of severe pain within from a few minutes to an hour or more after the bite of a spider has occurred. Not infrequently the patient is not conscious of having been bitten at all. The characteristic progress of the pain from the site of the bite to the abdomen is often overshadowed by the severity of the abdominal pain and ignored or forgotten by the patient. The pain may actually commence in the abdomen and remain localized there, though in such a

case it usually does radiate to the back or down the thighs, especially during the subsidence of the most acute symptoms. Nausea and vomiting frequently occur. There is characteristically an elevation of the patient's temperature to from 99 to 101 F. with an accompanying leukocytosis of from 12,000 to 20,000. The patient's pulse rate is usually elevated slightly, but in two of the cases of this series it was lower than normal. The blood pressure is usually elevated. Apparently, rigidity of the abdominal muscles, usually boardlike in character, is present in all cases. Palpation, however, reveals less tenderness than would be expected to accompany the rigidity. Morphine administered by hypodermic injection will relieve the pain partially though not entirely, but the rigidity of the abdominal muscles will not disappear after its use.

This summary of the syndrome shows how closely it may simulate an acute abdominal disease necessitating immediate surgical intervention. At a recent meeting of one of the prominent national surgical societies, a paper dealing with acute abdominal disease was read. During the discussion of the paper, a well known surgeon [2] mentioned a group of cases that he said always puzzled him greatly. He described two cases as typical examples. In each of them the symptoms, signs and laboratory findings were similar to those of arachnidism. In each instance the abdomen had been explored but nothing abnormal found except for an apparent spasm of the entire intestinal tract. For lack of a more satisfactory explanation he had ascribed the symptoms and signs to "enterospasm" of unknown origin. In some subsequent cases he had found that the administration of atropine hypodermically would relieve the symptoms. This was learned too late to try it in any of the cases of arachnidism of this report. Dr. Bryan has subsequently told me that he believes arachnidism to be very unlikely as the cause of the acute abdominal symptoms in at least some of his cases of "enterospasm."

While arachnidism has been discussed frequently and many cases have been recorded in the literature, I have found no reference to the syndrome in textbooks or periodicals devoted to surgery. In many of the recorded cases, however, the patient has been subjected to operation under a mistaken diagnosis.

A very comprehensive review of the literature was made by Bogen [3] in 1926. He added fifteen cases to those already reported and made several interesting observations. Apparently the age and sex incidence is unlimited. Some patients came from large cities while others dwelt in the country. Most of the bites occurred in the evening or early morning in the summer or early autumn.

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2. Bryan, W. A.: Personal communication.

3. Bogen, Emil: Arachnidism: Spider Poisoning, Arch. Int. Med. **38**:623 (Nov.) 1926.

Bogen stated that the Latrodectus mactans, frequently called the "black widow," is the chief and perhaps the only really poisonous spider in the United States. It has been found in almost all sections of the United States.

The following description is taken from his article:

Latrodectus Mactans is a shiny, coal black spider, usually brilliantly marked with red or yellow or both. The female, which is always the one responsible

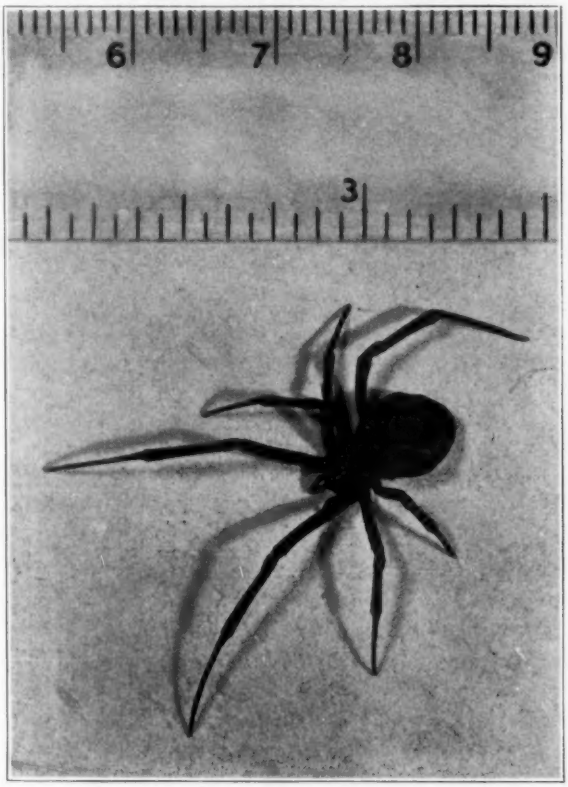


Fig. 1.—Female Latrodectus mactans caught beneath kitchen porch overhanging outside stairs to basement, Charlottesville, Va. (Hindmost left leg is missing.)

for the bites reported, is often a half inch in length when fully grown, and may stretch its slim, glossy, black legs over as much as 2 inches (5 cm.) [fig. 1]. The markings vary greatly, the most constant being a bright red patch shaped somewhat like an hourglass, on the ventral surface of the abdomen [fig. 2]. The globose abdomen, much larger than the cephalothorax, resembles a black shoe button, although it may have one or more red spots along the middle of the back and over the spinnerts, in addition to the ventral patch [fig. 3]. The male is much smaller than the female and is even more conspicuously marked, having four stripes along each side of the abdomen, in addition to the marks of the

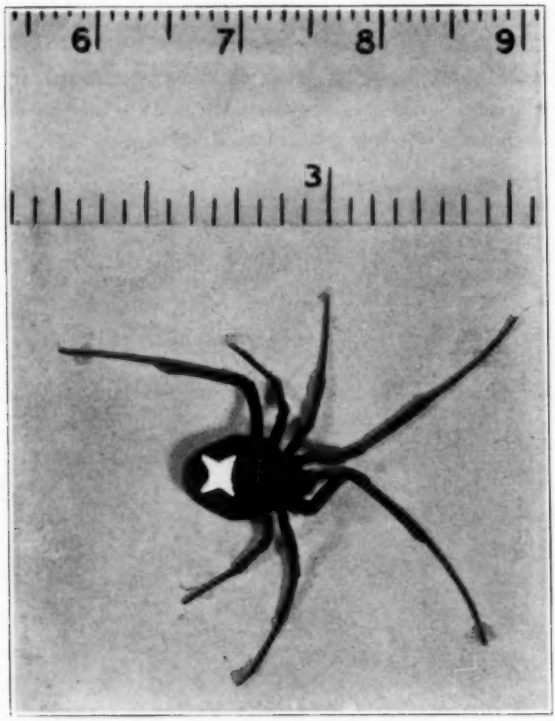


Fig. 2.—Female Latrodectus mactans, ventral aspect, showing "hour-glass," scarlet marking. (Outlined in white for clearer depiction.)

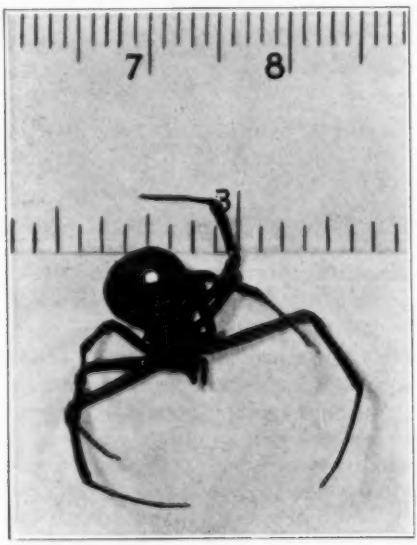


Fig. 3.—Female Latrodectus mactans, showing scarlet spot just cephalad to the spinnerts. (Outlined in white for clearer depiction.)

female. The young spiders are much lighter in color, gradually donning the glossy, black coat in a series of moults over about forty days.

The black widow, as it is called from its custom of eating its mate, is usually found alone, as it will engage in mortal combat with any other spider placed near it. It builds a coarse and irregular dark web in dimly lighted places where it may be undisturbed. Occasionally it is found under stones or pieces of wood or in holes in the ground, in old stumps or bushes, more often in the rafters and corners of little used buildings, in the basements and attics of unfrequented houses, and in the dark corners of barns and other outbuildings, and it has been frequently seen in outdoor toilets, where it builds its web across the seat of the toilet.

More than 150 cases of poisonous spider bites have been reported by thirty-three physicians in the United States during the last century. In several instances the patient was operated on by mistake for an acute appendicitis or other acute surgical abdominal disease, while biliary or renal colic, acute pancreatitis, ruptured gastric ulcer and various forms of poisoning were suggested in others.

Bogen, whose bibliography included 462 references, concluded that "arachnidism or spider bite poisoning is a true clinical entity in the field of general medicine." I might add that this clinical entity may be important to consider in the differential diagnosis of acute surgical abdominal disease.

SUMMARY

Six cases of arachnidism, poisoning from the bite of the Latrodectus mactans, or "black widow" spider, were reported. In some instances the spider bite had occurred without the patient's knowledge. The cases were characterized by the acute onset of very severe abdominal pain, usually nausea and vomiting, boardlike rigidity of the abdominal muscles with more or less tenderness and elevation in the patient's temperature and leukocytes. Attention was called to the ease with which the mistaken diagnosis of acute surgical abdominal disease might be made and the patient subjected to an unnecessary exploratory laparotomy. A previous comprehensive review of the literature by Bogen was briefly alluded to, including his statistics of the incidence of the disease and his description of the spider and its habitat. The importance of arachnidism as a clinical entity to be considered in the differential diagnosis of acute surgical abdominal disease was stressed.

# LIGATION OF THE SAPHENOUS VEIN

## A REPORT ON TWO HUNDRED AMBULATORY OPERATIONS

GÉZA de TAKÁTS, M.D.
AND
LAWRENCE QUILLIN, M.D.
CHICAGO

### PREVIOUS LITERATURE

In a previous communication one of us (Dr. de Takáts [1]) advocated ligation of the saphenous vein for certain types of patients afflicted with varicose veins. The operation was described as an ambulatory procedure to be used in combination with injection treatment. Since that time we have been able to perform this operation on one hundred and fifty more patients, and are now presenting a report on the total of two hundred cases, describing the indications and contraindications, the statistical data of our material, the technic, postoperative course and complications and the results and recurrences.

Celsus,[2] in his books on medicine, described an operation for varicose veins as follows:

> The skin over the vein being incised, the edges are taken up by a small hook and the vein is drawn apart on all sides from the body; and it is guarded against lest among these things themselves, it may be injured. And a blunted little hook is placed under, and about the same space being placed between (four fingers), the same is done in the same vein; whither it may tend is known easily, the little hook being extended. When the same has been done in whatever part varices are, the vein being drawn in one place by a little hook, is cut off; afterward in what part the next hook is, it is drawn and pulled out and there again is cut off. And thus on all sides the leg being freed from varices, then the edges of the wounds are closed together and an agglutinating plaster is cast on over.

Obviously, multiple excision of small segments of vein were made, but no mention is made of cautery or ligature to stop bleeding. Interesting notes about the etiology and operative treatment of veins are found in Ambroise Paré's work, published in 1579:

> The matter of them is usually melancholy blood, for varices often grow in men of melancholy temper and which usually feed on grosse meats or such as breed

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From the Peripheral Circulatory Clinic of the Department of Surgery, Northwestern University Medical School.

1. de Takáts, Géza: Ambulatory Ligation of the Saphenous Vein, J. A. M. A. **94**:1194 (April 19) 1930.

2. Celsus, A. C.: De medicina libri octo, Lugduni, Apud J. Tornæsium & G. Gazeium, 1554, book 7, par. 31.

grosse and melancholy humours. Also women with child are commonly troubled with them by reason of the keeping together of their suppressed menstrual evacuation. It is best not to meddle with such as are inveterate; for of such being cured there is to be feared a reflux of the melancholy blood to the noble parts, whence there may be imminent danger of maligne ulcers, a cancer, madnesse or suffocation.

Paré advocated tying the vein below the knee. The last two complications suggest a frequent occurrence of sepsis and pulmonary embolism, although the idea that the varicose blood was dangerous had already been expressed by Hippocrates. The formation of varicose veins was thought to be an effort of nature to sidetrack the deleterious humors that might otherwise cause madness, etc. This opinion was handed on intact until the discovery of circulation.

W. Turner Warwick [3] gave an excellent description of the gradual evolution of the mechanical theory as opposed to the humoral theory of Hippocrates. The mechanical theory of varicose veins was the consequence of Harvey's theory of circulation, and the importance of valves was gradually recognized.

So far as can be ascertained, Home [4] in 1801 practiced ligation of the saphena magna at the level of the knee, with the view of cutting off the column of blood from ulcers. "Within a few hours after the vena saphena has been taken up the symptoms disappear and the patient is led to take notice of the distress it before gave him and to explain the sense of the suddenness of its removal." The operation was condemned because of the frequent occurrence of sepsis. Brodie, cited by Warwick [2] in his lectures on "Surgery and Pathology," appreciated the value of Home's procedure, but he tried other measures of interrupting the continuity of the vein. He tried open division with a compress, whereas Colles devised a vein truss, and Velpeau a pin which passed underneath the vein with the two ends tied together above it.

This was the status of vein ligation when Trendelenburg,[5] in an aseptic era, revived the theory of reflux and established the operation on a rational basis, stating that the vena cava, the iliac vein and the trunk of the femoral vein below Poupart's ligament usually have no valves, and that if the saphenous valves become incompetent a single wide tubular system exists from the heart to the ankle. He also pointed out that the variations of intra-abdominal pressure would be trans-

3. Warwick, W. Turner: The Rational Treatment of Varicose Veins, and Varicocele, London, Faber & Faber, Ltd., 1931.

4. Home, Everard: Ulcers on the Legs, London, W. Buhmer & Company, 1801.

5. Trendelenburg, Friedrich: Ueber die Unterbindung der Vena saphena magna bei Unterschenkelvarizen, Beitr. z. klin. Chir. **7**:195, 1891.

mitted to the saphenous system. To protect this system, he advised saphenous ligature about 3 inches (7.6 cm.) above the knee. Later Perthes, from his clinic, emphasized high ligation at the saphenofemoral junction, as in seven of the seventy-eight cases collaterals developed above the ligature.

The end-results of Trendelenburg's operation were not encouraging. There were from 22 to 72 per cent recurrences reported,[1] so that the method, practiced alone, fell gradually into disrepute. In addition, the percentage of fatal embolism following this operation was estimated from a large personal series of Bernsten as 0.7 per cent. This astonishingly high percentage of embolism has kept many surgeons in constant fear of vein ligations. In reading the description of Trendelenburg's operation, we find that following vein ligation, the patient's legs are bandaged from the ankle to the site of ligature, and are splinted and immobilized for three weeks. These procedures, we fear, are not the proper measures to combat embolism, but are important factors in producing it.

On analyzing our results with the injection treatment for varicose veins,[6] we found a definite percentage of recurrences, which were due to recanalization of the obliterated veins because of an uninterrupted reflux from the proximal segments of the saphenous vein. Therefore, ligation of the saphenous vein was introduced as an adjunct to the injection treatment, preventing backflow, serving as a barricade to ascending phlebitis and reducing materially the number of necessary injections.[1] The combination of injection treatment with vein ligation was not new; Tavel,[7] Schiasis [7] and Moszkovicz [8] advised such a procedure. However, no emphasis has been laid on the importance of the ambulatory type of ligation. Aside from the economic aspect of saving the patient hospital expenses and permitting him to continue work after two days, we hope that the danger of embolism may be obviated or reduced to a minimum in the ambulatory patient.

No smaller authority than Theodor Kocher [9] had his patients get up the second day after a high saphenous ligation, which he combined with multiple percutaneous ligatures of Schede; sometimes as many as two hundred ligatures were employed on one patient. Such patients were allowed to get up the second day and were discharged on the

6. de Takáts, Géza, and Quint, Harold: The Injection Treatment of Varicose Veins, Surg., Gynec. & Obst. **50**:545 (March) 1930.

7. Cited by Sicard, J., and Gaugier, L.: Le traitement des varices par la méthode sclérosante, Paris, Masson & Cie, 1927.

8. Moszkovicz, Ludwig: Behandlung der Krampfadern mit Zuckerinjektionen kombiniert mit Venenligatur, Zentralbl. f. Chir. **54**:1732 (July 9) 1927.

9. Kocher, Theodor: Vereinfachung der operativen Behandlung der Varizen, Deutsche Ztschr. f. Chir. **138**:113 (Nov. 1) 1916.

fifth day. In our series not one patient, whether a dispensary or a private patient, has been hospitalized, and in the two hundred patients we have not observed a single embolism or pulmonary infarct.

### INDICATIONS AND CONTRAINDICATIONS

The preliminary report has already stated [1] that when the long saphenous vein is visible or palpable above the lower third of the thigh, the ligature is preferred to injections at this level. It is, of course, possible to make injections into the saphenous vein above this point or even just below Poupart's ligament and produce an obliteration of the vein, but there are several reasons why to us an aseptic ligature seems more advisable in such cases. First, injections are sometimes impossible above the middle of the thigh, because the vein dips deeper and deeper in the subcutaneous fat and may not be palpable at all in spite of existing valvular incompetence. In such patients, if injections are made at a lower level, an ascending thrombosis will make the previously unrecognizable vein suddenly manifest and palpable to the saphenofemoral junction. This progressive, ascending thrombus has none of the characteristics of the thrombus produced at the site of local intimal irritation. It is a stagnation thrombus (static thrombus of Aschoff), and is soft, friable and hardly adherent to the wall. Given the other possibility, that the vein is widely patent to its junction with the femoral vein and injections can be made into it, clots of formidable size, which have been seen to attain 5 cm. in width (fig. 1) cannot be regarded as harmless. The frequently expressed idea of McPheeters,[10] that embolism is not to be feared because of the reversed flow of blood in the varicose vein, refers only to the upright position; certainly in the horizontal position the pressure in the veins of the extremities is negative.

An equally important reason for advocating ligature of the saphenous vein at high levels is frequent canalization of thrombi if the backpressure of blood is permitted to persist. It was with the idea of diminishing the incidence of recurrences that the ambulatory vein ligation was proposed. The backpressure in previous measurements was as high as 210 cm. of water.[11] Our idea has been corroborated and extended by convincing histologic evidence through the significant work of Howard, Jackson and Mahon.[12] They reported the strikingly high

10. McPheeters, H. O.: Varicose Veins, ed. 3, Philadelphia, F. A. Davis Company, 1931, p. 71.

11. de Takáts, Géza; Quint, H.; Tillotson, I. T., and Crittenden, P. J.: The Impairment of Circulation in the Varicose Extremity, Arch. Surg. **18**:671 (Feb.) 1929.

12. Howard, M. J.; Jackson, C. R., and Mahon, E. J.: Recurrence of Varicose Veins Following Injection: A Study of the Pathologic Nature of the Recurrence and a Critical Survey of the Injection Method, Arch. Surg. **22**:353 (March) 1931.

incidence of 79 per cent recurrences caused by recanalization. That a totally occluding superficial thrombophlebitis may result in a recanalization of the vein has been seen in five personally observed cases. The double ligature with excision of a segment of at least 3 cm. in length is a permanent block, although a possibility of a "detour" will be discussed later.

In the first communication it has also been stated that the average number of necessary injections following ligation could be reduced from twenty-one to six. The same observation could be made in the present larger series.

Another indication for tying the saphenous vein has been an ascending thrombosis of a spontaneous phlebitis if one is able to ligate above the thrombosis. We have recognized this indication in five cases of acute ascending thrombophlebitis. The ligature not only acts as a barrier to the distal clot, but seems to alleviate the pain by removing the tension of backpressure from the inflamed vessel. These patients have not been strictly ambulatory, as they have been admitted to the hospital and kept in bed for a few days. However, as soon as the fever and pain subsided, they were allowed to get up, and they were home on the fourth day. In addition, other measures were used to hasten absorption of the periphlebitic exudate, the discussion of which is not within the scope of this paper.

The contraindications to ligation of the saphenous vein are few and definite. In the first place, if the venous dilatations are present only below the knee and the long saphenous vein is not palpable even at the level of the inner condyle, the operation is not necessary. Secondly, if there are multiple incompetent anastomoses between the deep and the superficial system, a high ligature of the saphenous vein will not prevent the inflow from the deep veins. In such patients an attempt may be made to make multiple ligations of the incompetent anastomoses. For such multiple ligations we prefer to admit the patient to the hospital for twenty-four hours, just for his comfort, but not with the idea of immobilizing him for any length of time. If there are too many incompetent valves, a high ligation followed by excision and stripping is our method of choice.[6]

Thirdly, the vein ligation is not indicated if a deep venous block is present. Men of great experience in this line, such as McPheeters, have stated that they have never seen a lack of patency in the deep vein. It is, of course, well known that a clot in the deep veins becomes permeable after a certain length of time either by a true canalization of the thrombus or by a reestablishment of circulation through short collaterals and the vasa vasorum. Nevertheless, following a deep venous thrombosis, a certain degree of venous insufficiency persists,

and the ligature of a compensatory dilatation does not seem logical. It may not aggravate the edema, but it will hasten the development of other collaterals. One must also consider the effect of old canalized thrombi on the important femoral valve at the level of Poupart's ligament, which protects the limb from backpressure.

G. P., aged 46, had a left-sided deep thrombophlebitis following childbirth. Twenty-six years later she was seen with a tortuous long saphenous vein, into which a large anterolateral branch emptied. The Trendelenburg test gave a positive result. The Perthes test showed deep patency. There was no edema. A high ligation of the saphenous vein was performed, and multiple injections were made into the thigh and calf distally to the ligation. The patient made an uneventful recovery; at the time of her discharge all the veins were obliterated. There was no edema. One month later, the vein into which injections were made was firmly obliterated, but a new large channel was visible, running parallel with the original vein. The vein started from above Poupart's ligament and was obviously not an overlooked saphenous branch. We have interpreted this recurrence as the result of increased venous pressure in the deep veins, which opened up new superficial veins.

To sum up, then, ligation of the saphenous vein is indicated: (1) in valvular incompetence of the long saphenous vein above the lower third of the thigh, (2) in valvular incompetence of the anastomotic branches, if they resist injection treatment and (3) in ascending thrombophlebitis of the saphenous vein.

The operation is contraindicated: (1) when the vein is not involved above the knee, (2) when there are multiple incompetent valves in the communicating branches which cannot all be ligated and (3) when there is evidence of insufficient deep venous return owing to an old deep phlebitis or a deep valvular insufficiency.

## TECHNIC OF AMBULATORY VEIN LIGATION

It would hardly seem necessary to describe a simple vein ligation in detail. Nevertheless, there are a few minor details that are significant because the operation is performed on ambulatory patients. The operations were done in a sterile operating room either at the hospital or in a perfectly equipped operating room of the surgical dispensary, with all necessary precautions such as masks and mouth pieces covering the nose. In the standing position the course of the vein is marked out with a 2 per cent solution of brilliant green. The skin is shaved dry just before the operation and prepared with ether, iodine and alcohol. The line of incision in high saphenous ligations runs about a handwidth distally and parallel to Poupart's ligament and should start mesially to the palpable femoral artery. Naturally, if the vein is palpable at this level, a shorter incision of from 3 to 4 cm. is sufficient. Generally we prefer transverse incisions, because thus some of the accessory saphenous branches are caught and tied. However, if a

longer segment of vein should be excised with its insufficient anastomotic branch, a longitudinal incision is more useful.

The line of incision is infiltrated with 0.5 per cent procaine hydrochloride with 3 drops of 1 : 1,000 epinephrine to each ounce (fig. 1). Only a superficial subcutaneous infiltration is made, and repeated aspirations are made for blood. Because of the vicinity of the large vein, care must be taken not to inject any procaine hydrochloride intravenously. In one patient, as reported in our previous article,[1] only a few drops of procaine hydrochloride were sufficient to produce pallor, tachycardia and numbness of the lips and fingers. The toxic effects wore off in a few minutes, but illustrate the necessity of extreme care in this region to avoid intravenous injection.

Figure 1

Figure 2

Fig. 1.—Ligation of the right internal saphenous vein. A week later a massive clot was palpated above the knee. The left side has not been treated.

Fig. 2.—The course of the vein is outlined in the standing position at the highest palpable point with a 2 per cent aqueous solution of brilliant green. Five-tenths per cent procaine hydrochloride solution with 3 drops of epinephrine, 1 : 1,000, is used to infiltrate a transverse line of incision. Beware of intravenous injection!

After waiting about five minutes for a complete anesthesia, incision is made through the skin and subcutaneous fat. In some patients a strong tortuous anterior branch lies immediately under the skin and needs no further exposure. This, however, may not be the main trunk, but a collateral from the superficial epigastric, overcoming a previous iliac block. At this high level (three fingerbreadths below Poupart's ligament) the main trunk lies below the superficial fascia and has to be exposed at a depth of from 2 to 4 cm., or sometimes even more. When the main vein is exposed, a perivenous injection is made on both sides of the vein as traction on the perivenous sympathetic fibers produces pain (fig. 2). A curved artery forceps

or aneurysm needle armed with no. 1 chromic catgut is insinuated under the vein twice (fig. 3). The two ligations are tied at a distance of 3 cm. or more, and the segment of vein is well lifted up to detect communicating branches from the deep veins, which should also be carefully tied as they may produce a profuse hemorrhage (fig. 4). It is important to place the proximal ligature as close to the femoral junction as possible, leaving a very short stump. As an added precaution a second ligature may be applied to the proximal stump, as considerable pressure is exerted on it in the ambulatory patient.

The segment of vein is then removed, and it is used for bacteriologic study. Before the wound is closed the patient is asked to cough a few times to catch, if

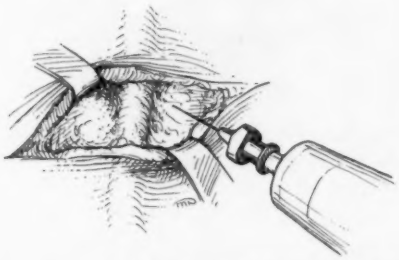

Fig. 3.—A short transverse incision is made through the skin, the subcutaneous fat and, if necessary, the superficial fascia. When the vein is exposed, a few drops of procaine hydrochloride are injected around it.

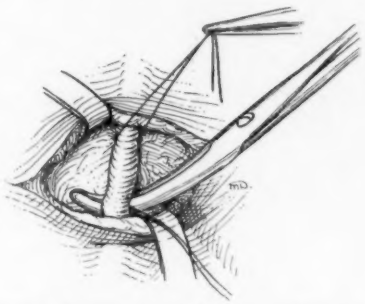

Fig. 4.—A curved artery forceps, carrying a number 1 chromic catgut ligature, is passed under the vein. The vein is lifted up, and another ligature is placed at least 1 inch proximal to the first one. The proximal ligature should be close to the saphenofemoral junction.

necessary, additional bleeders. No sutures are placed in the subcutaneous fat, and the skin is closed with interrupted dermal sutures. The skin around the incision is now painted with a mastic solution,[13] and the gauze is stuck to the skin with the solution (fig. 5). In ambulatory patients who perspire freely, sweat and dirt cannot be kept away from the incision with the usual adhesive tape bandage. This solution, which one of us has used exclusively since 1914 in all aseptic operations, keeps the skin around the incision dry and protected. We strongly emphasize its

13. Gum mastic, 40 Gm., benzene, 60 cc., castor oil, 20 drops; then add sufficient

use here, particularly in dispensary patients, who sometimes return with soiled and slipped dressings.

The patients return for inspection in forty-eight hours, and the stitches are removed on the eighth day. They are asked to stay away from work for the first two days and may return to work after the first inspection. They should not stay in bed during the day for any time.

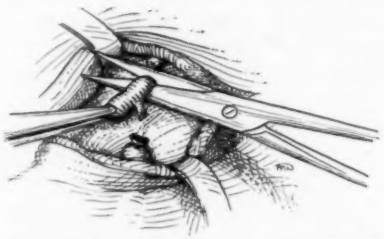

Fig. 5.—Both ligatures are tied. The segment of vein between the two ligatures is excised. No clamps are used at any time.

Fig. 6.—The bleeding is accurately controlled. Interrupted dermal sutures approximate the edges of the skin. The skin around the line of suture is painted with a solution of mastic in benzene, and a layer of gauze is stuck to the skin, which produces a water-tight dressing. Elastic compression is applied on top.

## ANALYSIS OF MATERIAL

*Age, Sex and Previous Treatment.*—This report is based on two hundred ambulatory vein ligations, performed on dispensary patients [14]

14. The operations were performed by Drs. Zimmermann, Jacques, Quillin and Quint, members of the Varicose Vein Clinic.

and in the private practice of the authors. The patients' ages, classified in decades, were as follows:

| Decades | Number of Patients |
|---|---|
| 10–20 | 2 |
| 20–30 | 30 |
| 30–40 | 69 |
| 40–50 | 58 |
| 50–60 | 34 |
| 60–70 | 5 |
| 70–80 | 2 |
| | 200 |

Ninety-five per cent of the patients were between 20 and 60 years of age, 1 per cent between 10 and 20 and 1 per cent between 70 and 80.

There were ninety-four female and one hundred and six male patients, illustrating, as has been pointed out before, that at least in our material there is no feminine prevalence.

As to occupation, all walks of life are represented, the majority of cases occurring in patients giving a history of long hours on their feet or hard manual labor in the upright position.

The influence of heredity, studied in a previous report,[6] was again very striking. Particularly significant seems the observation that whenever varicose veins are encountered in the young both parents were affected.

The previous treatment of these patients was as follows:

| | |
|---|---|
| 140 | Had had no previous treatment |
| 3 | Had had surgical excisions (but no high ligation) |
| 8 | Had worn Unna's casts |
| 49 | Had had injection treatment |
| 200 | |

Of the three surgical excisions, not one could be called radical, judging from the scars. The saphenous vein was not ligated below Poupart's ligament, and short scars were present on the calf and thigh. In the eight cases in which Unna's casts had been applied for varicose ulcers elsewhere, the patients were not progressing rapidly and there was a marked reflux of blood from above. Of greatest interest are the patients who had had injection treatment elsewhere or from us. It is this group that made us realize that the number of recurrences, reported elsewhere as 10 per cent, should be reduced by ligation. These patients fall into two groups: one in which obliteration was never accomplished (in one case as high as fifty injections were given) and another in which early recanalization took place. In the private practice of one of us, ligations in patients who had previously been given

injections became necessary seven times because of repeated recurrences. Since the ligations, recanalization has not occurred in this group.

The postoperative disability was estimated as follows (all patients were told to take one day off following the operation):

| Number of Patients | Disability |
|---|---|
| 161 | None |
| 22 | 1 day |
| 8 | 2 days |
| 3 | 3 days |
| 3 | 4 days |
| 1 | 8 days |
| 1 | 9 days |
| 199 | |

An analysis of patients who were disabled for more than two days will be made in the section on complications.

*Complications.*—One patient had a hemorrhage owing to the slipping of the proximal ligature. She was taken to a hospital, where the hemorrhage was controlled. The patient made an uneventful recovery. In one patient a hematoma developed, which produced a serous discharge for nine days and then healed up completely. In one patient a wound infection developed on the fourth day; the abscess was opened. The patient was not hospitalized, and the wound healed in eleven days.

One patient died of streptococcic septicemia. A wound infection developed in this patient, which was obvious on the fourth day, but for various reasons the patient could be hospitalized only on the tenth day, when he was admitted with a generalized streptococcic septicemia. Death occurred as a result of the infection. At autopsy no thrombosis of the proximal saphenous stump or of the femoral vein was found. Death occurred because of a surgical infection, which was localized but because of improper after-care resulted in a generalized infection.

One patient, whose case was reported in our previous series, had a slight procaine hydrochloride reaction during the operation owing to an intravenous injection of the drug. The toxic symptoms disappeared within a few minutes.

A tabulation of complications shows the following:

| | |
|---|---|
| Procaine hydrochloride reaction | 1 |
| Hematoma | 1 |
| Postoperative hemorrhage | 1 |
| Wound infection | 1 |
| Death from septicemia | 1 |

We believe that all of these complications are preventable, at least to a minimum. They have not occurred in our private work. The

procaine hydrochloride reactions will not be encountered if frequent, careful aspirations are made for blood before the drug is injected. Hematomas can be reduced to a minimum if all tributaries are carefully tied, if the patient is asked to cough or strain before closing the wound and if a tight pressure bandage is applied. Slipping of the proximal ligature occurred once; since that time, a double ligature has been placed on the proximal stump. Care must be exercised to leave a large enough segment of the vein distal to the ligature. The one death from septicemia was due to an initial surgical infection, which unfortunately still occurs in any large group of aseptic operations. It is probably unavoidable at the present time, although all operations were carried out under strict aseptic precautions, with masked head, nose and mouth. The measures that should be carried out, however, in all cases showing infection consist in immediate hospitalization, immobilization and hot wet dressings, with incisions when necessary.

Secondary infection from the skin in these ambulatory patients is also a possibility. We strongly emphasize the use of the glue, the mastic solution, which forms a watertight contact between the skin and dressing and prevents perspiration.

*Thrombosis Following Vein Ligation.*—Of the two hundred patients, sixty-five, an incidence of 32.5 per cent, showed a massive thrombosis distal to the ligature. Of this group, forty, that is, 20 per cent of the original two hundred, showed complete obliteration, which did not necessitate further injections. It seems obvious that it is in this group of patients who are cured after Trendelenburg's vein ligation, although none of the older statistics bring out this point, that the patients who have a distal thrombosis following the operation are the ones who remain cured. It is because of the comparatively frequent occurrence of distal thrombosis that we do not advocate injections at the time of ligation, as they may not be necessary or they may even activate a resting infection.[15]

The thrombosis following ligation may be purely static and aseptic, occurring in the form of a narrow, firm cord, with no inflammatory reaction around it, but more frequently it is accompanied by a massive periphlebitic exudate, which is hot and tender on pressure but does not lead to an elevation of temperature. Of the eight patients who were disabled more than two days, five belonged to this group. If the patients are given proper elastic support in the form of Unna's paste boot or an elastic adhesive bandage, they are comfortable. They should not be put to bed, but should be encouraged to be up and around, as we think that the ambulatory ligation is our real safeguard against embolism.

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15. de Takáts, Géza: The "Resting Infection" in Varicose Veins, Am. J. M. Sc. **184**:57 (July) 1932.

The thrombosis in the proximal stump is, of course, of even greater interest and has been carefully looked for in every case. The idea of some surgeons, that every vein ligation results in a massive clot proximal to the ligature, cannot be substantiated. If the vein is occluded with a ligature without first crushing it with artery forceps, the endothelial damage is small and nothing but a microscopic clot results. The classic experiment of Baumgarten, who showed that blood did not have to clot in the vein between two ligatures, should be recalled. If one could not tie a vein without the danger of embolism, surgeons would have to cease to operate entirely.

Of the two hundred vein ligations, there was a palpable clot in the proximal stump in eighteen (9 per cent). Occasionally a large varix at the level of Poupart's ligament, obviously above the saphenofemoral junction, would diminish in size or disappear. We have become more and more impressed with the facts, which have already been stressed by Margrit Hanselmann [16] in an inaugural dissertation, that the longer the proximal stump, the more apt is the proximal clot to appear, and that ligation close to the saphenofemoral junction is the best measure to avoid large clots in the proximal stump. Thus, aside from the ambulatory operations, the shortness of the stump is another safeguard against massive embolism.

Of the eighteen patients showing a proximal thrombosis, all but three had a distal thrombosis, which is suggestive of an increased endothelial reactivity of the patients. According to Dietrich, one of the foremost pathologists, the increased susceptibility of the endothelial lining is an important factor in thrombus formation.[17]

Whether it is possible to predict the occurrence of a distal or proximal thrombosis following vein ligation is an open question. Elsewhere one of us described simple methods of detecting resting infection previous to injection treatment.[15] The same procedures, namely, provocative vein puncture, diathermy or roentgen exposure, can be used to diagnose a latent infection or an increased susceptibility of the vein. However, such "flare ups" are much less frequent following ligation than after injections, because a ligature is much less irritating to the vein than an injection.

The occurrence of a proximal clot in 9 per cent of our cases makes one wonder why injections at high points would not be equally satisfactory so long as the ligature also produces a fairly large clot. We

16. Hanselmann, Margrit: Postoperative Thrombose und Embolie und ihre Prophylaxe, Inaug. Diss., Zurich, 1926.

17. Dietrich, A., and Schröder, K.: Abstimmung des Gefässendothels als Grundlage der Thrombenbildung, Virchows Arch. f. path. Anat. **274**:425, 1930.

have stated our standpoint in discussing the indications for ligation. The small aseptic clot, the permanent interruption of the venous channel with no chance of recanalization and the possibility of going up within an inch or less of the saphenofemoral junction and catching all branches not only make the operation safer, but also give a better prognosis so far as the end-results are concerned. The statement that the irritative thrombus is safer than the aseptic ligature thrombus because the former is more firmly attached holds only in cases in which the irritative thrombus is aseptic. Since, however, we have shown in our clinic that of fifty-eight clinically uninfected veins more than half gave a positive bacteriologic culture, we hesitate with injections for fear of a progressive thrombosis with inflammatory reaction. That the ligature can be safely applied under such conditions is best shown in patients whose veins have been tied during an acute ascending phlebitis with no reaction in either stump. The course of the five patients whose saphenous veins were tied during an acute attack of ascending superficial phlebitis was so satisfactory that such a procedure must always be considered, without prolonged immobilization.

*Results of Vein Ligation.*—In the present material a distinction must be made between the dispensary material (one hundred and thirty-five cases) and our private material. Both groups serve to elucidate important points.

The dispensary material contains eighteen patients who had previously been given injections elsewhere or by clinicians in our group, with no results. In these cases a total of two hundred and one treatments have been given with no obliteration, whereas following ligation the patients were discharged as cured after a total of fifty-seven treatments. The cases show such a striking effect of this operation on the right type of patients that we have tabulated the results individually (see the accompanying table). Patients 8 and 13 had partial excisions with stripping of the vein, but no high saphenous ligation. The veins were obliterated in six cases, eight injections being given following ligation. Patient 16 was treated with "many injections" elsewhere, so that the number of treatments is not included in the treatments preceding ligation.

We had originally hoped to present exact follow-up statistics of the entire material of two hundred cases. This was only possible of approximately one third of the dispensary material, although a real effort has been made by our social service department to have the patients appear for reexamination. In the private work of one of us it has been possible to secure exact data in 91 per cent of the cases in which operations were performed. The patients came in every three months for the first year, every six months the second year and

then once a year for the next three years. The first ambulatory vein ligation was performed in 1927; the first patient was under observation for four years.

As the dispensary material could not be adequately controlled for follow-up purposes, we shall limit ourselves to a discussion of the private cases, of which sixty exact records are available.

Of the sixty patients, in five a dilatation developed above the ligature. Four of these patients were operated on in 1927 or 1928, when ligatures were placed at the midthigh. Since then we have learned to insist on a high ligation at the saphenofemoral junction. One patient who had had a bilateral high ligation returned with a large dilatation at Poupart's ligament just above the scar, but only on the right side. The only

*Results of Vein Ligation Following Unsuccessful Injections*

| Patient | Number of Unsuccessful Treatments | Number of Treatments After Ligation | Follow-Up Notes* |
|---|---|---|---|
| 1 | 20 | 6 | Complete obliteration |
| 2 | 2 | 1 | Complete obliteration |
| 3 | 2 | 5 | No recurrence in 6 months |
| 4 | 10 | 0 | Total thrombosis |
| 5 | 5 | 3 | Excellent results; seen after a year |
| 6 | 6 | 2 | Complete obliteration |
| 7 | 14 | 1 | Excellent result |
| 8 | Vein stripping | 0 | Complete collapse |
| 9 | 11 | 6 | No record |
| 10 | 24 | 1 | Complete obliteration |
| 11 | 23 | 4 | No recurrence in 4 months |
| 12 | 2 | 4 | Complete obliteration; ulcers healed |
| 13 | Vein stripped | 9 | Complete obliteration |
| 14 | 7 | 2 | |
| 15 | 50 | 0 | Complete thrombosis |
| 16 | "Many injections" | 6 | Complete obliteration |
| 17 | 20 | 0 | Complete obliteration |
| 18 | 5 | 7 | Complete obliteration |
| | 201 | 57 | |

* The notes were made at least three months after operation. The patients were asked to return every three months for a year.

possible explanation was that this patient's femoral valve was deficient or absent, which fact was corroborated by the unusually strong impulse in this vein following coughing or straining. At reoperation a large, thin-walled, saccular dilatation was found between the proximal ligature and the saphenofemoral junction. This was completely excised, the new ligature being placed at the saphenofemoral junction. The exposed femoral vein showed such marked fluctuations to inspiration, coughing or sneezing that the diagnosis of the absence or incompetence of the femoral valve was certain. The significance of this anomaly must be investigated in other cases.

Recurrences caused by a marked reflux through incompetent perforating veins occurred only in two of the sixty patients (3 per cent). We have previously stated [6] that patients with large incompetent communications between the deep and superficial veins must have a radical

excision. Quite recently we have tried to ligate the incompetent perforating branches at the time the high saphenous ligation was done, but we cannot report any end-results at this time.

A summary of the recurrences following vein ligation combined with injections in sixty private cases is as follows:

| | |
|---|---|
| Dilatations proximal to the ligature (4 low ligations, 1 incompetent femoral valve) | 5 |
| Dilatations distal to the ligation (incompetent perforating veins) | 2 |
| | 7 |

The final analysis of these recurrences [18] indicates that high ligations should be done in every case, and that either the incompetent perforating veins should be ligated or a radical excision should be made. When one considers, furthermore, that patients who are submitted to vein ligation suffer from the most extensive and progressive type of varicose veins, the end-results show that the combination of vein ligation with injections offers in the suitable type of patient the best chances for permanent results.

*Embolism Following Vein Ligation.*—In the two hundred cases of ambulatory vein ligation we have not encountered any case of pulmonary embolism or ascending deep thrombosis. One cannot state that the operation is entirely free from this risk, because no operation is. We do believe, however, that two factors, namely, the ambulatory management and the shortness of the proximal stump, are important in the prevention of embolism. The classic description of ligation of the saphenous vein, which called for splinting and three weeks' immobilization in bed, showed the alarming percentage of 0.7 per cent of fatal pulmonary embolisms. When statistics will be available of at least one thousand ambulatory vein ligations, some statement may be made as to the frequency of this complication. We have good reason to believe, though, that they will compare favorably with minor ambulatory operations in this respect.

## CONCLUSIONS

On the basis of two hundred ambulatory vein ligations combined with the injection treatment for varicose veins, we think that this procedure has a definite place in the treatment for this condition. The high saphenous ligation protects the treated veins from fluctuations

18. These recurrences indicate that when ligation of the saphenous vein combined with injections was done with proper indications and proper technic a recurrence was found in one of sixty cases (0.6 per cent). This one recurrence was due to an incompetent femoral valve, a condition that we have overlooked entirely up to the present time.

of abdominal pressure and hydrostatic pressure, thus preventing canalization of the thrombi. It also reduces the necessary number of injections and places the occluding ligature close to the saphenofemoral junction. By insisting on a short proximal stump and on ambulatory management, we can report no embolism in the entire series. The complications reported in this series all seem avoidable with growing experience. The end-results of the operation combined with injections show a far smaller percentage of recurrences than those obtained with any other procedure in the treatment for varicose veins.

122 South Michigan Avenue.

# AVERTIN AS AN ANESTHETIC FOR GENERAL SURGERY

HENRY K. RANSOM, M.D.
ANN ARBOR, MICH.

In order to determine the worth as well as the limitations and dangers of the various new anesthetic agents, it is desirable that reports of many cases from different clinics be made. With this in view I have undertaken a critical analysis of the cases in which avertin was used either as the anesthetic or for basal narcosis supplemented with some form of inhalation anesthesia in the surgical clinic of the University of Michigan Hospital. This statistical survey covers the period from November, 1929 (when avertin was first adopted in this clinic), to January, 1932, and comprises 430 cases. Operations done in the divisions of genito-urinary and orthopedic surgery in which avertin was employed are included, but the cases in the neurosurgical field have been reserved for a separate report. While avertin was not used as a routine measure for any particular type of work, it was employed rather extensively in abdominal operations and also in operations performed on the face or about the mouth. In all of these cases considerable discretion was exercised in the selection of the patients. Ordinarily cachectic or very elderly persons as well as those greatly debilitated from chronic disease were excluded. In such patients the risk of pulmonary complications arising from a prolonged postoperative period of somnolence seemed to be unwarranted, and for them another anesthetic was usually selected.

## AGE AND SEX

The age according to decades and the sex incidence of the 430 cases are shown in table 1. The preponderance of men over women is of no significance as it simply reflects the fact that in this clinic there are more male than female surgical patients. While avertin was used fairly often for children, the instance of the patient 83 years old was an exceptional one. The average age of 36.2 years is an interesting figure, since it shows that fairly young and reasonably sound patients made up the majority of the group.

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From the Department of Surgery, University of Michigan.

DOSAGE

The dose in milligrams was in all instances calculated according to body weight. Table 2 shows the doses expressed in milligrams per kilogram which were employed. It will be noted that 110 mg. per kilogram was almost our standard dose. This was occasionally increased in some exceptional circumstances, and likewise on some occasions it was reduced. A dose of 110 mg. per kilogram has seemed to be satisfactory and safe, whereas at no time has it been my aim through either

TABLE 1.—*Age and Sex Incidence*

| | |
|---|---|
| **Age by Decades** | |
| 1-9 | 9 |
| 10-19 | 69 |
| 20-29 | 77 |
| 30-39 | 107 |
| 40-49 | 69 |
| 50-59 | 59 |
| 60-69 | 32 |
| 70-79 | 6 |
| 80-89 | 2 |
| Total | 430 |
| Youngest patient | 4 |
| Oldest patient | 83 |
| Average age | 36.2 years |
| **Sex** | |
| Males | 232=53.9% |
| Females | 198=46.1% |

TABLE 2.—*Dose of Avertin*

| Mg. per Kg. | Number Cases | Per Cent |
|---|---|---|
| 130 | 9 | 2.08 |
| 125 | 3 | 0.78 |
| 120 | 24 | 5.47 |
| 115 | 12 | 2.86 |
| 110 | 344 | 79.96 |
| 100 | 25 | 5.73 |
| 90 | 4 | 1.04 |
| 80 | 8 | 1.82 |
| 50 | 1 | 0.26 |
| Total | 430 | 100 |

the use of excessive doses of avertin or the use of heavy preoperative medication to produce complete surgical anesthesia without some form of reinforcement. The addition of a supplemental anesthetic such as nitrous oxide and oxygen or ether is without question a safer method. While 110 mg. per kilogram is a somewhat larger dose than that used by many surgeons, it has not seemed objectionable in my hands. When the smaller doses were employed, the results were considerably less satisfactory. With regard to children, my experience has been in accord with that of others, i. e., that they are more tolerant to avertin than adults, and even with doses of 110 mg. per kilogram, supplementary anesthesia was required in every case.

### ADMINISTRATION

Almost as a routine procedure the patients were narcotized in their own beds in the ward or private room. The general standard technic of administration recommended by the makers of the drug was followed. Cleansing enemas were given in the evening before the day of operation but ordinarily not on the operative day. Occasionally a mild sedative was given on that same evening. Most of the patients received some form of preoperative medication. This consisted for the most part of morphine sulphate, from $\frac{1}{6}$ to $\frac{1}{4}$ grain (11 to 16 mg.), or a mixture of opium alkaloids hydrochlorides, $\frac{1}{3}$ grain (22 mg.). Atropine was usually omitted, while rarely hyosine, from $\frac{1}{150}$ to $\frac{1}{100}$ grain (0.4 to 0.6 mg.), was used in conjunction with morphine. The calculated quantity, ranging approximately from 175 to 300 cc. of the 3 per cent solution of avertin which had previously been prepared by an expert pharmacist and kept at a temperature of 40 C., was administered by a nurse anesthetist. The fluid was introduced into the rectum through an ordinary male catheter with funnel attached and was allowed to flow in slowly by force of gravity. The ease of the induction and the absence of an excitement stage or struggling were noteworthy. The induced sleep seemed to resemble natural sleep more closely that that brought about by any other artificial means. The color of the patient was usually good, and there was an absence of marked sweating. Cyanosis was rarely noted. In from fifteen to thirty minutes the full depth of the narcosis was reached, and at or slightly before this time the patient was transported to the operating room. The transfer to the operating table, the preparation of the skin and the arrangement of drapings were carried out as usual. If cutaneous stimuli provoked a reflex response, a supplemental inhalation anesthetic was started at once. Otherwise, the operation was started and reinforcement resorted to when and if it became necessary.

### TYPES OF OPERATION

The various operations that were performed are shown conveniently grouped in table 3. It will be noted that considerable use was made of avertin in operations about the head or in the mouth as well as in the various abdominal operations. In the former type of operation, where gas masks or ether cones are apt to encroach on the operative field and so hamper the operator, an anesthetic substance that can be introduced into the circulation by way of the rectum has outstanding advantages. In the laparotomy group avertin gave important assistance in bringing about the requisite degree of muscular relaxation. The second column of figures in the table is of interest. It designates the number of cases in which no supplemental anesthetic was required and shows that this was chiefly in operations which did not involve opening the peritoneal cavity. It is of some interest that only 5, i. e., 12.5 per cent, of the

goiter operations (which ordinarily can be done under comparatively light anesthesia) were completed with avertin unassisted. This seems to bear out the observation that hyperthyroidism produces a greater tolerance to avertin, while conversely hypothyroidism is said to render a patient less tolerant and in such cases the dose should be correspondingly reduced. In keeping with this it was also frequently found that in using nitrous oxide and oxygen with avertin the ratio of the gases had to be kept at approximately the same level as in the cases in which no avertin was used.

TABLE 3.—*Operations under Avertin*

| Type of Operation | Total Number | Number Performed with Avertin Unassisted |
|---|---|---|
| Face and mouth | 68 | 40 |
| Hernia (all varieties) | 54 | 11 |
| Kidney and ureter | 47 | 10 |
| Gallbladder and biliary tract | 44 | 7 |
| Thyroidectomy | 40 | 5 |
| Appendectomy | 36 | 14 |
| Plastic | 21 | 5 |
| Exploratory laparotomy | 20 | 4 |
| Bone and joint | 19 | 5 |
| Resection cervical glands | 18 | 6 |
| Breast | 10 | 4 |
| Miscellaneous | 9 | 5 |
| Gastric resection | 9 | 4 |
| Gastro-enterostomy | 7 | 0 |
| Lumbar sympathectomy | 6 | 1 |
| Bladder and urethra | 5 | 0 |
| Colostomy | 4 | 2 |
| Amputation (thigh or leg) | 3 | 1 |
| Cholecystogastrostomy | 2 | 2 |
| Esophageal diverticulectomy | 1 | 1 |
| Duodenum | 2 | 1 |
| Pericardiotomy | 1 | 1 |
| Gastrostomy | 1 | 1 |
| Splenectomy | 1 | 0 |
| Lobectomy (pulmonary) | 1 | 0 |
| Gastrocolic fistula | 1 | 0 |
| | 430 | 130 |

## SUPPLEMENTARY ANESTHESIA

Table 4 indicates the number of the cases in which supplemental inhalation anesthesia was necessary. As will be noted, nitrous oxide and oxygen was the supplemental anesthetic of choice and was used in the great majority of cases. In 33 cases this alone was not sufficient, and a moderate quantity of ether vapor was given through the McKesson machine. The 21 cases in which ether alone was used for reinforcement call for some comment. These cases were of two types: The first group involved operations done inside of the mouth where anesthetic apparatus was objectionable. In these cases the avertin was supplemented at intervals with ether given through the ether vapor apparatus. The other group was composed of very major abdominal

procedures in which most complete muscular relaxation was necessary, such as lumbar sympathectomy and operations on the biliary tract or deep in the pelvis in muscular persons. A synergistic effect between avertin and ether was noted, and in many cases the ether was necessary only during the preliminary exploration of the abdominal cavity and the packing off process, and could be discontinued during the remainder of the operation with possibly a small quantity again for closure of the peritoneum. Thus the total quantity of ether would range from only ½ to 2 ounces in many of the cases, with nevertheless a high degree of muscular relaxation. When nitrous oxide with oxygen was the supple-

TABLE 4.—*Supplementary Anesthesia*

| | Number Cases | Per Cent |
|---|---|---|
| None | 130 | 30.23 |
| Gas | 246 | 57.21 |
| Ether | 21 | 4.88 |
| Gas and ether vapor | 33 | 7.68 |
| | 430 | 100 |

TABLE 5.—*Evaluation of the Anesthetic*

| | Number | Per Cent |
|---|---|---|
| Good | 235 | 54.64 |
| Satisfactory | 64 | 14.95 |
| Fair | 48 | 11.08 |
| Excellent | 42 | 9.79 |
| Very good | 25 | 5.93 |
| Poor | 16 | 3.61 |
| | 430 | 100 |

mental anesthetic, the percentage of oxygen in the mixture could usually be considerably increased. The average ratio of the gases used for this entire group was 82:18 which, of course, means that the percentage of oxygen is practically double the amount possible when used with nitrous oxide alone. Oftentimes the percentage of the oxygen in the mixture was considerably higher than this, starting with a 90:10 ratio of the gases and tapering off to perhaps a 50:50 ratio at the conclusion of the operation.

## EVALUATION OF THE ANESTHETIC

In table 5 an attempt has been made to evaluate the quality of the anesthesia. At the conclusion of each operation the operating surgeon was requested to state his opinion of the anesthetic for that particular case. The opinions expressed show that in about 86 per cent of the cases the anesthesia was entirely satisfactory, while in slightly less than 14 per cent it was thought to be only fair or poor.

BLOOD PRESSURE CHANGES DURING AVERTIN ANESTHESIA

In the entire number of cases, careful recordings were made of variations in blood pressure, both systolic and diastolic, as well as changes in the pulse and respiration during the course of the operation. In each case a basal blood pressure reading was taken before the administration of the avertin. There was considerable variation in this initial pressure among the different patients, the highest systolic reading being 210 mm. of mercury and the lowest 72, with an average systolic pressure of 120. Of the diastolic recordings, the highest that was noted was 140 and the lowest 20, with an average diastolic pressure of 72. After the administration of the avertin it was ordinarily noticed that there was a moderate decline in pressure during the first fifteen or twenty minutes; the pressure then gradually rose again, and at the conclusion of the operation was approximately at the preoperative level. In most

TABLE 6.—*Stimulants During Operation*

| Stimulants | Number | Per Cent |
|---|---|---|
| None | 360 | 83.77 |
| Caffeine | 47 | 11.00 |
| Ephedrine | 9 | 2.09 |
| Both | 14 | 3.14 |
| | 430 | 100 |
| Intravenous dextrose | | 7 |
| Blood transfusion | | 5 |

cases this preliminary drop in blood pressure was not sufficient to cause concern, and there were no attendant objectionable symptoms such as cyanosis or marked changes in the pulse. In case the drop in pressure was extraordinary or tended to be prolonged, it was found that this could be satisfactorily counteracted by the use of ephedrine or epinephrine. In general, it seemed that the administration of some inhalant, such as ether, nitrous oxide or carbon dioxide, aided considerably in bringing up a lowered blood pressure. Table 6 shows the incidence of the use of the various stimulants during the course of the operation. The cases noted in which intravenous dextrose or blood transfusion was required were cases in which the nature of the operation made these expedients necessary, and it was through no possible fault of the anesthetic that they were required. Likewise, the rather large number of cases in which caffeine was given is not a true index of the actual necessity for stimulation consequent on the anesthetic. It was more or less customary at the conclusion of the operation, if the patient was still profoundly narcotized, to administer an ampule of caffeine in order to shorten somewhat the postoperative reaction time. On the whole, my experience would not tend to show that the fall in blood pressure

from the use of avertin was highly objectionable, and it certainly does not seem comparable either in magnitude or as a cause for alarm with the changes in blood pressure that occur during the use of spinal anesthesia. After the administration of the avertin, blood pressure readings were taken at ten minute intervals during the course of the operation. As stated before, the maximum fall in pressure usually occurred from ten to thirty minutes after the introduction of the avertin, and these changes may be summarized as follows: Of the 430 cases followed, in 17, or 4 per cent, there was no initial change in systolic blood pressure. In 357 cases, or 83 per cent, there was a decline in systolic pressure, and in 56 cases, or 13 per cent, there was an actual initial rise in pressure. In the cases showing a decline in systolic pressure the average decrease amounted to —28 mm. of mercury, or a drop of 23 per cent, while

TABLE 7.—*Changes in Blood Pressure*

| | | | Number Cases | Per Cent | Average Amount, Mm. Hg. | Per Cent | Total Average, Mm. Hg. | Per Cent |
|---|---|---|---|---|---|---|---|---|
| Systolic | Initial | No change | 17 | 4 | .... | .... | | |
| | | Increase... | 56 | 13 | +28 | +23 | —20 | —17 |
| | | Decrease.. | 357 | 83 | —28 | —23 | | |
| | Final | No change | 39 | 9 | .... | .... | | |
| | | Increase... | 163 | 38 | + 2 | + 1.7 | — 5 | — 4 |
| | | Decrease.. | 228 | 53 | — 2 | — 1.7 | | |
| Diastolic | Initial | No change | 34 | 8 | .... | .... | | |
| | | Increase... | 91 | 21 | +17 | +24 | —10 | —14 |
| | | Decrease.. | 305 | 81 | —19 | —27 | | |
| | Final | No change | 65 | 15 | .... | .... | | |
| | | Increase... | 189 | 44 | +15 | +21 | +0.3 | +0.4 |
| | | Decrease.. | 176 | 41 | —15 | —21 | | |

those showing a rise in systolic pressure showed an average increase of + 28 mm. of mercury, or a rise of 23 per cent. The total average initial systolic change amounted to — 20 mm. of mercury, or a drop of 17 per cent. Regarding the initial change in diastolic pressure, of the 430 cases there was no initial change in 34, or 8 per cent. In 305 cases, or 71 per cent, there was a decrease in pressure and in 91, or 21 per cent there was an increase. The amount of these changes is as follows: The average decrease for the 305 cases was — 19 mm. of mercury or a 27 per cent fall, while the average increase in the 91 cases showing an initial rise was + 17 mm. of mercury, or a 24 per cent increase. This gave a total average initial change of — 10 mm. of mercury or a fall of 14 per cent. At the conclusion of the operation the following changes in pressure were noted: Of the 430 cases, the systolic pressure was at the preoperative level in 39, or 9 per cent. In 228, or 53 per cent, it was still below the preoperative level, while in 163 cases, or 38 per cent, it was above the basal reading. Of the cases in which there was a final decrease in systolic pressure, the average

amounted to — 2 mm. of mercury, or 1.7 per cent. Of those showing an increase, the average increase was + 2 mm. of mercury, or 1.7 per cent, while the total average systolic change was — 5 mm. of mercury, or a 4 per cent drop. Final diastolic changes were as follows: Of the 430 cases, 65, or 15 per cent, showed no change; 176 cases, or 41 per cent, showed a decline and 189 cases, or 44 per cent, showed an increase. Of those showing a decrease, the average decline was — 15 mm. of mercury, or 21 per cent, while the average increase in those showing a rise was + 15 mm. of mercury, or 21 per cent, and the total average diastolic change was negligible. Table 7 summarizes these changes in blood pressure.

### CHANGES IN PULSE AND RESPIRATION

Changes in the pulse rate following the administration of avertin were also studied. Of the 430 cases, 30, or 7 per cent, showed no

TABLE 8.—*Changes in Pulse and Respiration*

| | | Number Cases | Per Cent | Average Number Beats | Total Average |
|---|---|---|---|---|---|
| Pulse | Increase | 262 | 61 | +19 | +7 |
| | Decrease | 138 | 32 | —16 | |
| | No change | 30 | 7 | .... | |
| Respiration | Increase | 305 | 71 | + 9 | +6 |
| | Decrease | 60 | 14 | — 4 | |
| | No change | 65 | 15 | .... | |

change in pulse rate after the administration; 138 cases, or 32 per cent, showed a decrease in the pulse rate, while 262, or 61 per cent, showed an increase. The average increase in those showing an elevation in pulse rate was + 19. The average decrease in those showing a drop was — 16, while the total average pulse change was + 7. The changes in respirations were: Three hundred and five cases, 71 per cent, showed an increase in the respiratory rate; 60 cases, 14 per cent, showed a decrease in the respiratory rate, while 65, 15 per cent, showed no change. The average increase in the respiratory rate of those showing a rise was + 9, and the average decrease in those showing a decline was — 4. The total average change in respiratory rate was +6.

### NAUSEA AND VOMITING

The incidence of postoperative nausea and vomiting is of interest. In 267 cases, or 62 per cent, nausea and vomiting were entirely absent. In 163 cases, or 38 per cent, there were some nausea and vomiting after operation. For the most part these were very transient and ordinarily could be ascribed to the operation itself rather than to the anesthetic, and in none of the cases were nausea and vomiting greatly prolonged, as one occasionally sees after deep ether narcosis.

### REACTION TIME

Of particular interest was the time required for reaction. Table 9 shows in a statistical way the time interval between the conclusion of the operation and the time when reaction took place. It will be noted that in a small group of 10 cases the patients reacted immediately after the operation, while approximately 23 per cent of the patients reacted in less than one hour. The largest group was composed of 204 patients, or 47 per cent of the total number. These patients reacted between one and three hours, whereas the next largest group reacted between three and six hours, and a comparatively small number required more than six hours for reaction. The longest reaction time recorded was eighteen hours, and the second longest period fifteen hours. Further mention of the two patients who died without reacting will be made

TABLE 9.—*Reaction Time*

| Time | Number | Per Cent |
|---|---|---|
| Immediate | 10 | 2.48 |
| 2 to 15 min. | 44 | 10.25 |
| 15 min. to 1 hr. | 45 | 10.56 |
| 1 to 3 hr. | 204 | 47.52 |
| 3 to 6 hr. | 104 | 24.22 |
| 6 to 12 hr. | 16 | 3.73 |
| Over 12 hr. | 5 | 1.24 |
| | 428 | 100 |
| Died without reacting | 2 | |
| | 430 | |

Average reaction time—2½ hr.

later. The average reaction time as computed for all of the cases amounted to two and one-half hours. At the present time, I am trying the effect of withdrawal of the residual avertin solution from the rectum at the conclusion of the operation. Following this, a rectal instillation of oil is given. While no definite data are as yet available on the results, there is some evidence to show that the reaction time can be further shortened in this manner. After reacting, the patients were ordinarily drowsy for several hours longer but could be readily awakened for the administration of fluids. In our opinion, there was no increase in the necessity for postoperative catheterizations. A striking and advantageous feature was the subsequent amnesia for this postoperative period.

### POSTOPERATIVE COMPLICATIONS

A complete tabulation of all complications arising during convalescence was made. Table 10 lists the major nonfatal complications which were found and also the time of their appearance. Of especial interest in this connection is the group of cases in which postoperative pulmonary complications developed which might be attributed to the

anesthetic. On the assumption that such complications will make their appearance within five days after operation, the cases in which there were pulmonary complications that might be charged to avertin are marked with an asterisk. The first 4 cases in the table fall into this category. They consisted of 2 cases of bronchitis, 1 of pleurisy and 1 of bronchopneumonia. All of the patients recovered under the usual treatment. Case 257443, in which a nephrectomy was done for renal tuberculosis, was that of a patient with other associated tuberculous

TABLE 10.—*Postoperative Complications*

| Case No. | Age | Sex | Operation | Anesthetic Combination | Complications | Time of Development After Operation |
|---|---|---|---|---|---|---|
| 266266* | 29 | M | Inguinal herniotomy and orchidopexy | 110 mg. per Kg. and gas | Pneumonia | 2nd day |
| 265910* | 50 | M | Spinal fusion | 110 mg. per Kg. alone | Pleurisy | 2nd day |
| 276750* | 43 | M | Cholecystectomy and appendectomy | 110 mg. per Kg. and gas | Bronchitis | 4th day |
| 265890* | 29 | F | Cholecystectomy and appendectomy | 110 mg. per Kg. and ether | Bronchitis | 3rd day |
| 250033 | 40 | F | Cholecystectomy and appendectomy | 110 mg. per Kg. and gas | Pulmonary infaret or bronchopleurisy at base of right lung | 2 wk. |
| 261776 | 37 | F | Cholecystectomy | 110 mg. per Kg. and ether | Respiratory paralysis | Immediately |
| 255423 | 75 | M | Colostomy for carcinoma of rectum | 110 mg. per Kg. and gas | Heart block (advanced myocarditis) | 2nd day |
| 257443* | 34 | F | Nephrectomy for tuberculosis | 115 mg. per Kg. and gas | Bronchopneumonia? tuberculous | 2nd day |
| 269856 | 47 | M | Cholecystogastrostomy for carcinoma of pancreas | 110 mg. per Kg. alone | Pleurisy with effusion | 11th day |
| 278866* | 33 | M | Drainage of appendical abscess | 110 mg. per Kg. and gas | Respiratory paralysis | 2nd day |
| 238818 | 36 | M | Abdominal sympathectomy | 130 mg. per Kg. alone | Postoperative mania (psychogenic) | For 2 wk. |

lesions, and the pneumonia, which developed on the second postoperative day, was thought possibly to be a tuberculous pneumonia. The acute condition cleared up promptly, but the patient was placed on the usual regimen ordinarily prescribed for patients with pulmonary tuberculosis. Case 270866 must be included among the pulmonary complications. This patient, shortly after being returned to the ward following operation, had a temporary respiratory arrest, for no clear reason. Under appropriate treatment he was resuscitated, and the remainder of the convalescence was without event. In case 261776 likewise, temporary paralysis occurred. Here, however, it was thought that this was due to a slip in the ward routine. The patient, who had had a preliminary dose of morphine and hyoscine before the administration of the avertin, was returned to the ward following

operation in good condition but still deeply narcotized. On her return, through a misunderstanding of orders, the nurse in charge at once administered ¼ grain of morphine subcutaneously. Shortly after this there was a cessation of respiration, although the pulse remained practically normal. Artificial respiration was instituted at once, and after a period of about fifteen minutes normal respiration again took place, and there was nothing further to mar the convalescent period. This undoubtedly was due to an error in management, and it was felt that had the additional morphine not been given this complication could have been averted.

In the entire series there was no evidence of rectal irritation or ulceration from the use of avertin in any case. No case was discovered in which there was bleeding or discharge from the rectum, and no symptoms such as rectal pain or discomfort were encountered following the use of avertin. This we attribute to the fact that great care was exercised in the preparation of the solution, as it seems to have been satisfactorily proved that the early cases in which such complications ensued were undoubtedly due to the fact that either decomposed preparations or solutions of improper $p_H$ value were used.

Likewise, there was no evidence that repeated administrations of the drug were attended with additional danger. Several instances occurred in the series in which avertin was used repeatedly without ill effect. One man in the course of a year had nine plastic operations, all done with avertin, and a woman with gallstones, who refused operation, received six full sized doses in a period of two weeks for the control of intolerable pain.

### DEATHS

In the 430 cases, there were 22 deaths, or a mortality of 5.1 per cent. It can be readily seen from table 11 that in most instances the deaths were due to causes other than the anesthetic, and for the most part the fatal issue took place a considerable time after the operation was performed. The cases in which the anesthetic may have been or probably was a factor have been marked with an asterisk and might be mentioned individually. Case 272390 undoubtedly must be classified as one of death due to avertin. This patient had a laparotomy for what proved to be an inoperable carcinoma of the stomach with abdominal carcinomatosis. The operation consisted of exploration only. He left the operating room in satisfactory condition but failed to react and died suddenly five hours later. Autopsy showed no positive cause for the sudden death. The most striking observation was a rather intense pulmonary edema.

In case 263327 the patient was a frail little woman with an adenomatous goiter and a damaged myocardium. It will be noted that

the avertin dosage was considerably decreased below the average dose used in the series, and the patient awakened promptly at the conclusion of the operation. However, bronchopneumonia developed, proved by roentgen examination, probably on the basis of postoperative atelectasis, and this proved to be fatal in twenty-four hours.

TABLE 11.—*Number of Deaths*

| Case No. | Age and Sex | Operation | Anesthetic Combination | Cause of Death | Time of Death After Operation |
|---|---|---|---|---|---|
| 259041 | 48 F | Ventral hernia and fecal fistula | 120 mg. per Kg. alone | Generalized sepsis | 7 wk. |
| 269951 | 47 F | Nephrectomy for calculus, pyonephrosis | 110 mg. per Kg. alone | Empyema bronchopleural fistula (16th day) | 18th day |
| 275073 | 62 M | Anterior gastro-enterostomy for carcinoma of stomach | 120 mg. per Kg. and gas | Renal insufficiency | 13th day |
| 254336 | 25 F | Duodenojejunostomy | 110 mg. per Kg. alone | Ulceration at anastomosis site and hemorrhage | 8th day |
| 263643 | 33 M | Multiple compound fracture of mandible and maxilla | 130 mg. per Kg. alone | Fat embolism of lung | 1 hr. |
| 273841 | 46 M | Lobectomy of upper and middle lobes for carcinoma of bronchus | 110 mg. per Kg. and gas | Pulmonary gangrene | 2 days |
| 277839 | 38 M | Ligation of internal jugular and ablation of sigmoid sinus for sigmoid sinus thrombosis | 110 mg. per Kg. and gas | Cavernous sinus thrombosis | 13 days |
| 257273 | 18 M | Reamputation of thigh for septic knee | 110 mg. per Kg. and gas | Bronchopneumonia | 33 days |
| 255786 | 34 F | Left nephrolithotomy | 110 mg. per Kg. and gas | Pyelonephritis | 3 wk. |
| 267018 | 27 F | Splenectomy for purpura hemorrhagica | 110 mg. per Kg. and gas | Continued hemorrhage | 3 days |
| 257655 | 57 M | Polya resection for gastric ulcer | 110 mg. per Kg. | Renal insufficiency and urinary suppression | 5 days |
| 270669 | 23 M | Thigh amputation for tuberculosis of the knee | 110 mg. per Kg. alone | Widespread tuberculosis | 41 days |
| 270308 | 69 F | Billroth II for carcinoma of stomach | 110 mg. per Kg. alone | Intestinal fistula | 15 days |
| 191783 | 65 M | Sublingual abscess, endothermy | 110 mg. per Kg. alone | Septicemia | 6 days |
| 272390* | 49 M | Exploratory laparotomy for carcinoma of stomach with carcinomatosis | 110 mg. per Kg. and gas and ether vapor | Did not react | 5 hr. |
| 252395 | 33 F | Ureterostomy for carcinoma of bladder | 110 mg. per Kg. and gas and ether vapor | Metastatic carcinoma and pyelonephritis | 22 days |
| 263327* | 55 F | Thyroidectomy for adenomatous goiter | 80 mg. per Kg. and gas | Atelectasis and bronchopneumonia | 24 hr. |
| 278395* | 57 M | Gastrostomy for carcinoma of esophagus and tracheo-esophageal fistula | 110 mg. per Kg. alone | Extensive carcinoma; did not react | 24 hr. |
| 278243 | 57 M | Polya resection for carcinoma of stomach | 110 mg. per Kg. alone | Peritonitis | 14 days |
| 216624* | 56 M | Metastatic carcinoma of neck glands (primary in tongue); excision of glands with ligation of internal carotid artery | 110 mg. per Kg. and gas | Right hemiplegia (2nd day after operation; bronchopneumonia (5th day after operation) | 8th day |
| 279539 | 52 F | Cholecystostomy for carcinoma of gallbladder with stones and empyema of gallbladder | 110 mg. per Kg. and ether | Duodenal fistula (carcinoma) | 29th day |
| 273282 | 53 F | Bilateral ureteral transplant and cystectomy for carcinoma of bladder | 110 mg. per Kg. alone | Cardiac failure | 2nd day |

In case 278395, the patient was an extremely emaciated man who had a cancer of the esophagus complicated by a tracheo-esophageal fistula. While his condition was desperate, a gastrostomy seemed to be clearly indicated. This operation is ordinarily performed under local anesthesia, but in this particular case avertin was chosen in order that a satisfactory examination of the trachea with biopsy might be carried out. This patient also failed to react from the avertin narcosis and died twenty-four hours later. An autopsy was not obtained.

In case 216624, the patient was a man with an extensive metastatic carcinoma of the cervical glands for which a radical resection was done. In the course of the operation it became necessary to ligate the internal carotid artery with the unfortunate consequence that a hemiplegia developed on the second postoperative day, and on the fifth day there was definite evidence of bronchopneumonia from which the patient died on the eighth day.

In case 273841, the patient was a man with carcinoma of the right primary bronchus. In doing a lobectomy of the upper and middle lobes, the main pulmonary artery was accidentally tied, which accounted for the gangrene of the lower lobe, which proved to be fatal on the second postoperative day.

Considering these two tables together, there were 8 cases of post-operative pulmonary complications, for the occurrence of which the anesthetic probably played a part. This gives a percentage of postoperative pulmonary complications of 1.9 per cent. Of these post-operative pulmonary complications, there were 4 frank pneumonias, giving a percentage of 0.9 per cent for the entire series. Of the postoperative pneumonias, 2 were fatal, giving a percentage of 0.5 per cent for the entire series, and of 50 per cent for the postoperative pneumonias.

## SUMMARY

The results from the use of avertin in this series of selected cases were on the whole highly satisfactory. The easy induction was one of the outstanding features and one that made avertin particularly agreeable to the patients. Avertin proved to be of especial value in operations on the head and face, in which many times it was possible to dispense completely with cumbersome apparatus such as gas masks or ether cones. Perhaps its sphere of greatest value was in abdominal surgery where, when combined with some supplemental anesthetic agent, it aided considerably in enhancing muscular relaxation. We are not prepared to advocate it as having any decided advantages in thyroid surgery. While it is admirably suited to the "steal" type of operation, it has not seemed that the quality of the anesthesia in these cases was importantly better when avertin was employed, and there are objections

both theoretical and actual to a prolonged period of somnolence after operation in this type of case. In such cases it seems particularly desirable to avoid abolition of the cough reflex, when mucus is apt to accumulate in the throat and attendant laryngeal edema is often present.

## CONCLUSIONS

1. A representative group of 430 surgical cases in which avertin was employed for anesthesia or basal narcosis has been analyzed.

2. The quality of surgical anesthesia produced by avertin unassisted or supplemented by gas or ether in most cases is entirely satisfactory. The induction from the standpoint of the patient is probably less unpleasant than that attendant on any other form of anesthetic.

3. In this series some form of supplemental anesthetic, such as nitrous oxide and oxygen or ether, was required in approximately 70 per cent of the cases, the operation in the remaining 30 per cent being performed without reinforcement.

4. While there was usually a preliminary fall in both systolic and diastolic blood pressure, this did not seem to be sufficient to cause alarm, and at the conclusion of the operation the pressure had practically reached the preoperative level. Falls in blood pressure were satisfactorily combated with ephedrine or epinephrine.

5. When nitrous oxide and oxygen were employed as a supplemental agent, the percentage of oxygen in the mixture could be increased to practically twice the amount possible when used with nitrous oxide alone. Likewise, if ether was used to supplement the avertin, the total quantity employed during the operation was considerably less than would have been required for straight ether anesthesia.

6. The average reaction time was two and one-half hours. The majority of the patients reacted between one and three hours, while about 23 per cent reacted in less than one hour.

7. Of the 22 operative deaths occurring in the series, only 4 seemed to have any definite relation to the type of anesthesia. In the entire series there were only 8 cases of postoperative pulmonary complications which seemed in any probability attributable to the avertin. Of these 8 cases of postoperative pulmonary complications, 4 were of pneumonia, and of these 4 postoperative pneumonias, 2 were fatal.

8. In order to avoid unnecessary dangers, it seems that considerable care should be exercised in selecting cases. If this is done, avertin, in my opinion, is not only a safe but an important addition to the anesthetic armamentarium.

# SPLENECTOMY IN THE TREATMENT OF HEMORRHAGIC PURPURA

JOHN MARTIN ASKEY, M.D.
AND
CLARENCE G. TOLAND, M.D.
LOS ANGELES

Thrombocytopenic purpura hemorrhagica is characterized clinically by pathologic hemorrhage, ranging from a massive loss in the acute form, usually with a rapid termination, to the milder form, lasting for years. The blood platelets or thrombocytes show marked reduction. Until recently, splenectomy in the fulminating form was considered contraindicated and futile. Killins,[1] Reuben and Claman [2] and others, however, have reported recoveries from the acute form following splenectomy.

The success of splenectomy in the majority of cases of the chronic form is conceded. A certain number of failures are reported, and these are difficult to explain. Giffin and Holloway [3] found no clinical or hematologic improvement in 4 of their 28 cases. Spence,[4] out of 101 cases abstracted, found 15 per cent with a return of symptoms.

The commonly accepted theory for the successful results after splenectomy regards the spleen as abnormally destructive to platelets, producing thrombocytopenia and its sequelae. The whole reticulo-endothelial system is diseased, and the spleen exerts the greatest destructive influence. Better results follow splenectomy performed on persons with the largest spleens and seem to corroborate this idea. Removal of the spleen usually is followed in a few hours by a marked rise in the blood platelets, and rarely is there postoperative bleeding. The great bulk of reticulo-endothelial tissue is represented by the spleen, and its extirpation usually is adequate. Return of symptoms theoretically should suggest increased activity or hyperplasia of the remaining reticulo-endothelial tissue.

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1. Killins, W. A.: Acute Thrombocytopenic Purpura Cured by Splenectomy, J. A. M. A. **92**:1832 (June 1) 1929.

2. Reuben, M. D., and Claman, L.: Splenectomy in Acute Thrombocytopenic Purpura Hemorrhagica, Arch. Pediat. **45**:84 (Feb.) 1928.

3. Giffin, H. Z., and Holloway, J. K.: A Review of Twenty-Eight Cases of Purpura Hemorrhagica in Which Splenectomy Was Performed, Am. J. M. Sc. **170**:186 (Aug.) 1925.

4. Spence, A. W.: Results of Splenectomy for Purpura Hemorrhagica, Brit. J. Surg. **15**:466 (Jan.) 1928.

That the return of symptoms is often due to an unnoticed accessory spleen is suggested by Morrison, Lederer and Fradkin.[5] They described a patient whose spleen was removed, but in whom a small accessory spleen was allowed to remain. Improvement was immediate but transient, and in a year the patient was bleeding again. They suggested hypertrophy of the remaining accessory spleen as an explanation. They believe the relative frequency of supernumerary spleens, often situated in aberrant abdominal foci, can account for many unsatisfactory results. They enjoin a careful search for accessory splenic tissue during splenectomy.

On the other hand, many patients show clinical improvement, with relief from hemorrhagic symptoms, and still fail to show satisfactory improvement in the hematologic findings. The platelets may remain low, the bleeding time prolonged, the tourniquet test positive and the blood clot nonretractile and still the patient will show no spontaneous ecchymosis, oozing gums or other hemorrhage from the mucous membranes.

### DIFFERENTIAL DIAGNOSIS

The differential diagnosis between purpura hemorrhagica and other blood dyscrasias when typical is comparatively sure, save in some fulminating types. Aplastic anemia, in the bleeding stage, is characterized by extreme anemia, marked leukopenia and reduction of the granulocytes, with no splenomegaly. Acute leukemia, especially if in the aleukemic stage and without peripheral adenopathy, may present difficulties. There may be splenomegaly, but the differential count of the white cells will usually show immature lymphocytes and lymphocytosis. In acute purpura hemorrhagica, the red count at the onset is not usually markedly reduced, anemia occurring in proportion to the loss of blood. The hemophilic person shows marked prolongation of the coagulation time and a normal bleeding time.

### ATYPICAL HEMORRHAGIC DISEASE

Recent literature has been instructive in showing the many atypical cases of hemorrhagic disease that occur. Glanzman,[6] Rothman and Nixon,[7] Minot [8] and others described a familial type of purpura hemorrhagica without thrombocytopenia. A normal platelet count is associated

5. Morrison, M. D.; Lederer, M., and Fradkin, W. Z.: Accessory Spleens, Their Significance in Essential Thrombocytopenic Purpuric Hemorrhagica, Am. J. M. Sc. **176**:672 (Nov.) 1928.

6. Glanzman, E.: Hereditäre hämorrhagische Thrombasthenie, Jahrb. f. Kinderh. **88**:1 and 113, 1918.

7. Rothman, P. E., and Nixon, N. K.: Familial Purpura Hemorrhagica Without Thrombopenia, J. A. M. A. **93**:16 (July 6) 1929.

8. Minot, G. R.: A Familial Hemorrhagic Condition Associated with Prolongation of the Bleeding Time, Am. J. M. Sc. **175**:301 (March) 1928.

peculiarly with a prolonged bleeding time, a nonretractile clot and a positive tourniquet test. The patients have all the clinical phenomena of purpura hemorrhagica. The platelets in this condition are believed to be qualitatively defective; hence the term "thrombasthenic" purpura in distinction to thrombocytopenic purpura.

In addition to one of the familial types, Giffin [9] reported another case, in a patient aged 9, with all the features of hemorrhagic purpura except thrombocytopenia. Bleeding from the mucous membranes occurred, with a prolonged bleeding time and a nonretractile clot but a normal number of platelets. Splenectomy was done, without the usual prompt improvement such as follows typical purpura hemorrhagica.

Sweeney [10] reported an atypical case in which the diagnosis was extremely difficult. Clinically, the patient had marked hemorrhages, but despite a greatly prolonged bleeding time the platelets were not reduced. The white cells were normal. He was given numerous transfusions of blood, but failed to improve, and as a last resort a splenectomy was done. There was a slight transient rise in the white cells, but no increase in the platelets and no improvement clinically. The patient died about six months later.

Kennedy [11] described the case of a child aged 4, with a prolonged bleeding and coagulation time, decreased platelets, intense anemia and slight leukocytosis. A splenectomy was done without improvement. Two months later tonsillectomy was followed by excessive hemorrhages and death. Necropsy revealed an aplastic bone marrow. The patient had an atypical aplastic anemia. Splenectomy in the cases reported by Giffin and Kennedy for familial thrombo-asthenic purpura hemorrhagica has not given the satisfactory results obtained in pure thrombocytopenic purpura. Little and Ayres [12] reported a death following splenectomy in a case of hereditary hemorrhagic purpura with a normal platelet count.

The most careful scrutiny of all patients with hemorrhagic disease is indicated before splenectomy is resorted to. Many cases are not typical, and the differential diagnosis is most difficult. In borderline cases with no improvement, splenectomy is perhaps justifiable if the hemorrhage is unrelieved by transfusion and death seems otherwise inevitable. The cases of acute bleeding, as described by Kennedy [10] and Killins,[1] were of this type. In the chronic type of bleeding with

9. Giffin, H. Z.: Unusual Types of Hemorrhagic Disease, Am. J. M. Sc. **175**:44 (Jan.) 1928.

10. Sweeney, J. S.: Chronic Aplastic Anemia and Symptomatic Purpura Hemorrhagica Probably Due to Benzol Poisoning, Am. J. M. Sc. **175**:317 (March) 1928.

11. Kennedy, R. L. J.: Diseases of Children Benefited by Splenectomy, J. A. M. A. **91**:874 (Sept. 22) 1928.

12. Little, W. D., and Ayres, W. W.: Hemorrhagic Diseases, J. A. M. A **91**:1251 (Oct. 27) 1928.

ecchymoses, bruising and moderate anemia we believe that it is better to postpone splenectomy unless the following requisites are met: (1) splenomegaly; (2) thrombocytopenia; (3) prolongation of the bleeding time; (4) nonretractility of the blood clot; (5) positive tourniquet test showing decreased capillary resistance; (6) normal coagulation time and (7) a normal or slightly increased leukocyte count.

The following case illustrates the clinical recovery following splenectomy in typical chronic hemorrhagic purpura, without, however, a hematologic recovery.

### REPORT OF A CASE

Miss M. S., aged 36, reported that at the age of 14 she noticed numerous spots on the legs about the size of a dime or greater, occurring without any bruising or injury. She was nicknamed "Spotty" by her playmates. At the age of 16 she was bitten on the arm by a mosquito, and a black and blue spot about 2 inches (5 cm.) in diameter developed at the site. At 19 she had an acute, severe pain in the lower part of the abdomen and fainted. In college she noticed that the discharge during her menstrual periods became profuse. Occasionally, a severe spontaneous vaginal hemorrhage developed.

In 1920, tonsillectomy was advised in the belief that the purpura was possibly due to infection. She lost a great deal of blood, and it was thought she would not live. Transfusion of blood was not resorted to, and the bleeding finally was stopped by clamps.

In October, 1922, she had another acute attack of abdominal pain associated with vomiting, believed to be acute appendicitis. She was seen by a physician, and for the first time was told that she had purpura hemorrhagica. Splenectomy had not yet been established in America as accepted treatment, and she forsook regular medical care for osteopathy. Brill and Rosenthal's[13] paper, in 1923, brought splenectomy a more generalized recognition, although Kaznelson[14] had reported the first case in 1916.

In 1923, she had a severe uterine hemorrhage.

In the summer of 1928, she had another attack of severe abdominal pain, during which she became very faint and weak. There was no external bleeding, but she became so anemic that she was given her first transfusion of blood. About this time, she first noticed a little oozing of blood from the gums and observed blood spots on her pillow in the morning.

In August, 1929, she was seized with griping abdominal pain, and vaginally passed several clots of blood. She had marked bleeding from the gums, the bleeding continuing for thirty-six hours. The vaginal bleeding finally was stopped by packing. She was seen at the office on Aug. 27, 1929. The skin was markedly pale, the mucous membranes washed out. A number of ecchymoses were present on the arms and legs. The spleen was enlarged two fingerbreadths below the costal margin. Changes in the blood typical of chronic thrombocytopenic hemorrhagic purpura were present and splenectomy was advised. She had another attack

13. Brill, N. E., and Rosenthal, N.: Treatment by Splenectomy of Essential Thrombocytopenia (Purpura Hemorrhagica), Arch. Int. Med. **32**:939 (Dec.) 1923; The Curative Treatment by Splenectomy of Chronic Thrombocytopenic Purpura Hemorrhagica, Am. J. M. Sc. **166**:503 (Oct.) 1923.

14. Kaznelson: Wien. klin. Wchnschr. **29**:1451, 1916.

of severe pain in the lower part of the abdomen and menorrhagia the next month; after its cessation she was admitted to St. Vincent's Hospital on November 1.

She was bleeding from the gums, and numerous suggillations were present on the body. The site of a hypodermic injection became swollen and discolored. The

TABLE 1.—*Changes in the Blood in Our Case of Purpura Hemorrhagica*

| | Red Blood Cells in Millions | Hemoglobin, per Cent | Leukocytes in Thousands | Polymorphonuclear Leukocytes, per Cent | Platelets in Thousands | Bleeding Time, Minutes | Clot Retractility | Tourniquet Test |
|---|---|---|---|---|---|---|---|---|
| Before splenectomy | | | | | | | | |
| 90 days | 4.4 | 25 | 9.7 | 61 | ... | .. | Negative | Positive |
| 13 days | 3.0 | 20 | 6.4 | 74 | 50 | 20 | Negative | |
| 8 days | 3.1 | 25 | 5. | .. | ... | 20 | ..... | Positive |
| 8 days | Direct transfusion—500 cc. whole blood | | | | | | | |
| 4 days | 3.5 | 30 | 4.6 | 79 | 80 | | | |
| 2 days | Direct transfusion—500 cc. whole blood | | | | | | | |
| 2 days | 3.8 | 34 | 5 | 78 | 150 | 14 | | |
| | Splenectomy followed by transfusion—500 cc. blood | | | | | | | |
| After splenectomy | | | | | | | | |
| 1 day | 4.4 | 42 | 57 | 94 | 177 | | | |
| 2 days | ... | .. | 55 | 96 | 160 | 4.5 | Present | Negative |
| 4 days | 4.2 | 39 | 33 .. | 87 | | | | |
| 6 days | 4.2 | 38 | 25 | 86 | 310 | .. | Present | Negative |
| 9 days | 4.2 | 41 | 16.5 | 80 | 380 | | | |
| 15 days | 4.4 | 46 | 17 | 78 | 250 | 4 | | |
| 20 days | 4.4 | 45 | 14 | 79 | 240 | | | |
| 27 days | 4.4 | 50 | 12.7 | 80 | 280 | 4 | | |
| 6 months | 3.8 | .. | 15 | 64 | 190 | 5 | | |
| 9 months | 3.9 | 35 | 19.1 | 58 | ... | 3 | | |
| 11 months | 5.8 | 59 | 16 | 52 | | | | |
| 13 months | 4.9 | 67 | 18 | 68 | | | | |
| 18 months | 4.7 | 65 | 15 | 58 | 29 | 2.5 | Absent | Positive |

TABLE 2.—*The Main Changes in the Blood in Hemorrhagic Disease*

| | Purpura Hemorrhagica | | Aplastic Anemia | Acute Leukemia | Hemophilia |
|---|---|---|---|---|---|
| | Acute | Chronic | | | |
| Splenomegaly | Not usually | Present | Not present | Variable | Not present |
| Anemia | Proportionate to bleeding | Proportionate to bleeding | Marked anemia before bleeding | Proportionate to bleeding | Variable, depends on loss of blood |
| White blood cells | Normal or increased | Normal or increased | Marked leukopenia | Leukemic normal or aleukemic | Normal |
| Differential blood study | Normal | Normal | Granulocytopenia | Atypical immature lymphocytes | Normal |
| Bleeding time | Increased | Increased | Increased | Increased | Normal |
| Blood platelets | Reduced | Reduced | Reduced | Reduced | Normal count |
| Coagulation time | Normal | Normal | Normal | Normal | Markedly prolonged |
| Heredity | May be familial type | May be familial type | Negative | Negative | Familial |

bleeding time was twenty minutes, the platelet count, 50,000. She was given a transfusion of whole blood on November 10 and again on November 12, with only slight improvement in the bleeding time. Splenectomy was done on November 14, followed by an immediate tranfusion, which was given as a precautionary measure, as there was no postoperative bleeding from the wound.

The pathologic report by Dr. E. M. Hall was as follows:

"The spleen is about two and one-half times normal size, and measures 15 by 9 by 5 cm. The capsule is smooth. There is a deep fissure near the upper third. The cut surface has a meaty appearance, the marking is indistinct, and the consistency firm.

"Sections stained with Giemsa show moderate, diffuse fibrosis, marked congestion, marked hypertrophy and hyperplasia of the endothelial cells of the venous sinuses. The venous spaces also contain a few polymorphonuclear leukocytes and an occasional eosinophil and normoblast. The diagnosis is chronic purpura hemorrhagica."

Clinically, there was a complete disappearance of oozing from the gums and purpuric spots the day after splenectomy. The blood changes are shown in the chart and table. About the sixth postoperative day, the patient complained of a rheumatic pain in her left shoulder, and signs of fluid gradually developed in the left pleural cavity. On the fourteenth postoperative day, a temperature of 101 F. developed. The chest was tapped on December 1, and 1,500 cc. of red turbid fluid was removed. This proved to be sterile. Following this the fever dropped, and there was no recurrence. She was discharged in good condition one month after splenectomy.

## COMMENT

This case illustrates the rather typical response of the blood picture to splenectomy. A tremendous leukocytosis, due to proliferation of the granular leukocytes, was found the day after splenectomy. This slowly decreased, but a year later the white cell count was still elevated. The frequency with which this is found after splenectomy for purpura hemorrhagica suggests the existence of a leukotoxin in addition to the supposed lysin that destroys the platelets. The persistent leukocytosis is unexplainable. Evans,[15] in reporting the blood changes following splenectomy, found no persistent leukocytosis. The white cells were usually normal within a month.

The slower rise in platelets, reaching the maximum about the eighth day after operation, is characteristic. The response, however, was moderate, the count failing to rise to the frequent level of from 500,000 to 1,000,000.

The immediate return to normal of the bleeding time after splenectomy was coincident with the rise of platelets. Over a period of a year and a half since the operation, there has occurred a gradual reduction of the platelets, but despite this, the clinical improvement has continued. There has been a gain in weight and strength. The patient is again teaching.

The end-result of the splenectomy as seen a year later was a clinical cure, but only moderate hematologic improvement. The so-called essential factor in the production of the disease, thrombocytopenia, had

15. Evans, W. H.: The Blood Changes After Splenectomy in Splenic Anemia, Purpura Hemorrhagica and Acholuric Jaundice, with Special Reference to Platelets and Coagulation, J. Path. & Bact. **31**:815 (Oct.) 1928.

reappeared, but the usual sequel, pathologic hemorrhage, had not. The blood clot again failed to retract; there was a shower of petechiae on application of the tourniquet, but no oozing of the gums or menorrhagia. Again, atypically and peculiarly, the bleeding time was normal.

That there is an additional factor responsible for the disease other than the thrombocytopenia is indicated by this and other reports. Apparently, clinical hemorrhagic purpura can appear when the platelets are normal in number, as in the "thrombasthenic" type, usually familial. Conversely, a patient may have a marked reduction of the blood platelets without clinical purpura hemorrhagica.

It follows that the sole explanation for the clinical cure of purpura hemorrhagica in the majority of cases by splenectomy cannot be the postoperative elevation of the platelets. It is concomitant with improvement, but the effect of splenectomy is more complex and far-reaching than it has yet been possible to explain.

## SUMMARY

The salient facts in the literature concerning so-called chronic essential thrombocytopenic purpura have been reviewed. A number of atypical cases of unusual hemorrhagic disease have been cited, and the futility of treatment for such cases by splenectomy pointed out. The necessity for a meticulous scrutiny of all hemorrhagic patients to eliminate atypical cases such as "thrombasthenic" purpura is suggested.

A case showing a clinical recovery but a hematologic failure is described. Thrombocytopenia apparently is not the only factor operating in purpura hemorrhagica.

# PASSAGE OF CHOLESTEROL THROUGH THE MUCOSA OF THE GALLBLADDER

A. L. WILKIE, M.D.
AND
HENRY DOUBILET, M.D.
MONTREAL, CANADA

For the past number of years the question of the etiology of cholesterosis of the gallbladder has assumed widespread interest.

In a series of 5,000 gallbladders removed at operation, MacCarty,[1] in 1919, found cholesterosis of the gallbladder to be present in 18 per cent of his cases. In 1921, Mayo[2] found cholesterosis in 39 per cent of 1,254 cases of disease of the gallbladder. Mentzer[3] in 1926 published autopsy reports of 612 cases, with an incidence of cholesterosis as high as 38 per cent. In 1929, Illingworth[4] noted cholesterosis in 21 of 100 consecutive gallbladders removed at operation.

Anywhere from 20 to 50 per cent of these cases of cholesterosis were associated with gallstones, usually composed of pure cholesterol.

Cholesterosis, so named by Mentzer[5] in 1925, is a pathologic condition of the mucosa of the gallbladder, consisting macroscopically of tiny yellowish granules lying beneath the epithelium. Microscopically, in a Sudan-stained section, lipoid material may be seen deposited at the bases of the epithelial cells and in the large mononuclear endothelial cells of the stroma. In the majority of cases the subepithelial coat appears thickened by a varying amount of fibrous connective tissue. Very often scattered areas of small round cells may be seen. As a result of the combined fibrosis and the excessive deposits of lipoid material, the so-called "villi" of the mucosa are, as a rule, found to be shortened and thickened, but occasionally may be elongated and bulbous, or even definitely papillomatous in appearance.

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1. MacCarty, W. C.: Ann. Surg. **69**:131, 1919.
2. Mayo, C. H.: Minnesota Med. **4**:1, 1921.
3. Mentzer, S. H.: Surg., Gynec. & Obst. **42**:782, 1926.
4. Illingworth, C. F. W.: Brit. J. Surg. **17**:203, 1929.
5. Mentzer, S. H.: Am. J. Path. **1**:383, 1925.

Virchow first noticed what he considered to be cholesterol in the mucosa of the gallbladder in 1857. Moynihan in 1909 described the macroscopic condition aptly named by MacCarty the "strawberry" gallbladder. It remained for Boyd,[6] however, in 1922, to show that the yellow material found in the wall of the gallbladder in these conditions was undoubtedly cholesterol. He demonstrated that the normal dried mucosa of the gallbladder contained about from 0.5 to 1 per cent of cholesterol, whereas the dried mucosa of the strawberry gallbladder could contain as much as 60 per cent of the substance.

Although various authors have differed in their opinions as to whether inflammation plays any part in the production of cholesterosis, Illingworth [4] has shown experimentally that by feeding rabbits a high cholesterol diet and at the same time producing a chronic cholecystitis, it is possible to obtain a lesion that corresponds closely to that of cholesterosis in the human being.

Mentzer believes cholesterosis to be essentially a metabolic disturbance. Blaisdell and Chandler [7] were able to produce what they believed to be a cholesterosis of the gallbladder by merely administering a high cholesterol diet to animals.

Since 1906, Aschoff [8] has insisted that cholesterol is absorbed by the mucosa of the gallbladder, having proved experimentally that neutral fats and fatty acids could be easily absorbed. However, he was never able to show any direct proof of the absorption of cholesterol. Torinoumi,[9] by reinjecting a measured quantity of bile into gallbladders in which the cystic ducts had previously been ligated and analyzing this bile from seven to thirty-eight days afterward, produced results that tended to confirm Aschoff's belief of the absorption of cholesterol.

Boyd also believes that cholesterol is absorbed by the mucosa of the gallbladder.

Illingworth [4] injected suspensions containing 3,442 mg. of cholesterol per hundred cubic centimeters of bile into the gallbladder of cats, after tying the cystic duct, and showed that under these conditions a part of the cholesterol was absorbed from the gallbladder. It must be remembered, however, that this concentration of cholesterol is about ten times as great as that which normally occurs in the bile in the gallbladder, and that the medium used was an artificial one.

Naunyn,[10] on the other hand, always considered that the cholesterol of the bile was derived from the mucosa of the biliary passages and

6. Boyd, W.: Brit. J. Surg. **10**:337, 1922.
7. Blaisdell, F. E., and Chandler, L. R.: Am. J. M. Sc. **174**:492, 1927.
8. Aschoff: München. med. Wchnschr. **37**:1847, 1906.
9. Torinoumi: Beitr. z. path. Anat. u. z. allg. Path. **72**:456, 1924.
10. Naunyn, B.: Mitt. a. d. Grenzgeb. d. Med. u. Chir. **33**:2, 1921.

gallbladder. His opinion, however, was not based on any direct experimental evidence.

The recent experimental work of Elman and Graham [11] seems to favor the latter view, since their evidence indicates that cholesterol is secreted into the bile in the gallbladder.

It may therefore be seen that two main theories exist as to the origin of cholesterol deposited in the wall of the gallbladder in so-called cholesterosis, and in order to understand the condition in which cholesterol plays so important a part, it is necessary at the outset to determine the function of the normal gallbladder in regard to cholesterol.

Most of the workers in the past have experimented with cholesterol in an artificial suspension and in abnormal concentrations. It has been the aim throughout the present work to use as much as possible the normal concentration of cholesterol as found in animal bile.

The purpose of the following experiments is to determine whether cholesterol passes through the wall of the gallbladder from the bile into the blood stream or lymphatics, or, vice versa, from the blood stream into the bile.

## TECHNIC

The technic of the experiments was as follows:

A fistula of the common duct was produced in a dog after the method of McMaster.[12] A cholecystectomy was performed; the common duct was cut across, and a cannula was placed in the proximal end. A soft rubber tube was attached to the cannula and led down to a U-shaped tube in the animal's pelvis, whence a second firmer tube was carried through the abdominal wall to a sterile rubber balloon. The object of the U-shaped tube was merely to prevent any tension on the cannula in the common duct. In this way sterile bile from the common duct could be collected when necessary.

In this series of experiments all animals were treated in the same fashion. The operative procedure was carried out as follows:

Under ether anesthesia the dog's abdomen was opened. The cystic duct was carefully isolated and ligated, special care being taken not to include the cystic blood vessels or lymphatics, especially the main trunks of the latter, which course down in the fatty tissue on the inferior aspect of the duct.

The bile was then aspirated through the fundus of the gallbladder by a no. 14 blunt cannula inserted by means of a trocar, which was withdrawn as soon as the gallbladder was pierced. The gallbladder was emptied as completely as possible. Saline was not used to wash out the lumen, as the experience of some experi-

11. Elman, Robert, and Graham, E. A.: The Pathogenesis of the "Strawberry" Gallbladder: (Cholesterosis of the Gallbladder), Arch. Surg. **24**:14 (Jan.) 1932.

12. McMaster: Studies from Rockefeller Institute for Medical Research, 1924, no. 51, p. 107.

menters has shown that such procedure rapidly tends to injure the delicate mucosa. On the other hand, it was found that by ordinary aspiration practically all the bile could be removed and that only a small amount clinging to the mucosa remained.

The amount of bile aspirated was measured and replaced by an equal quantity of bile derived from a fistula of the common duct of another dog, as described. The opening in the fundus was closed by a fine purse-string suture in such a way as to evert the mucosa. A sample of the bile from the common duct was set aside in each case for a quantitative estimation of cholesterol. It was therefore possible to know the exact quantity of cholesterol that was injected into the lumen of the animal's gallbladder. For convenience, this dilute bile from the common duct is termed "A bile."

At the end of twenty-four hours, the animal was killed and the liver, gallbladder and common duct were removed intact. This was done in order to be certain that the cystic blood vessels were not included in the ligature around the cystic duct, and that no accessory bile ducts were communicating with the gallbladder. If either of these errors was found, the experiment was discarded.

If the blood vessels were found intact and the gallbladder was completely isolated, the biliary contents were carefully removed into a small beaker. This was done in such a fashion as not to scrape the mucosa, so that a small portion of the thick inspissated bile was invariably left adherent to the mucosa.

The bile was constantly found to be dark, inspissated and partly precipitated at the end of twenty-four hours. Approximate measurements showed it to be concentrated from two to three times its original volume. This thick viscid bile removed at the end of twenty-four hours is termed the "B bile."

By estimating the total quantity of cholesterol in the A bile and comparing it with the total quantity in the B bile, values are obtained which throw definite light on the cholesterol function of the normal gallbladder during the process of concentration of hepatic bile.

Analysis of the bile cholesterol by the colorimetric method described in the literature was found to be difficult owing to the yellow discoloration present in the extracts. Eventually the method employed was as follows:

A measured quantity of bile was placed into a 100 cc. beaker, and 10 cc. of 20 per cent potassium hydroxide was added. The contents were heated in a water bath for thirty minutes, and 10 cc. of a 30 per cent calcium chloride solution was then slowly added, with constant stirring. Plaster of paris was then added and thoroughly mixed with the contents, which were then dried at 55 C. Extraction was carried out for ten hours in a Soxhlet apparatus, anhydrous ether being used. The ether containing the cholesterol was then poured into a small beaker and the flask rinsed three times with small quantities of fresh ether. After the ether had evaporated at room temperature, the dry residue was extracted with hot chloroform and an appropriate portion of this compared colorimetrically by the Burchard-Lieberman reaction against a standard solution of cholesterol. By the addition of known amounts of cholesterol to the bile, the loss by this method was never more than 6 per cent.

However, as colorimetric estimations of cholesterol are regarded with some doubt by certain investigators, in dogs V, VII and VIII, the estimations of both A and B biles were carried out by the digitonin method exactly as described by

Gardner.[13] Portions of the A biles in these three cases were also determined by the colorimetric method, with the following results:

| | Colorimetric | Digitonin |
|---|---|---|
| V A | 10.86 mg. | 8.85 mg. |
| VII A | 15.47 mg. | 14.17 mg. |
| VIII A | 6.58 mg. | 6.45 mg. |

This correlation between the two methods indicates that the colorimetric method used is sufficiently reliable for our purpose. Most investigators have found the colorimetric method to yield slightly higher results than the digitonin method.

## EXPERIMENTAL DATA

The results of the experiments are as follows:

*Dog I.*—After the cystic duct had been ligated, 10 cc. of hepatic bile derived from the biliary fistula of another dog was injected into the gallbladder. Ten cubic centimeters of this bile was found to contain 3.58 mg. of cholesterol. At the end of twenty-four hours, the animal was killed and the gallbladder removed. Only 2 or 3 cc. of thick, dark viscid bile (B bile) was found inside the gallbladder; on analysis, this material was found to contain a total of 5.46 mg. of cholesterol. This represents in twenty-four hours an increase of 1.88 mg., or 52 per cent, of cholesterol in the contents of the gallbladder. Two facts must be noted: in the first place, only 10 cc. of bile was introduced, and secondly, the A bile had a fairly high cholesterol concentration, 35.85 mg. per hundred cubic centimeters of bile.

*Dog II.*—In a similar way, this animal had 31 cc. of hepatic bile (A bile) containing 7.05 mg. of cholesterol introduced into the gallbladder. At the end of twenty-four hours, estimation of the contents of the gallbladder showed a total of 28.69 mg. of cholesterol, an increase of 21.64 mg., or 307 per cent. In this case three times as much A bile was used as in the previous animal, and in addition the concentration of cholesterol in the A bile was much less, being only 22.75 mg. per hundred cubic centimeters of bile.

*Dog III.*—Twenty-nine cubic centimeters of hepatic bile, containing 5.69 mg. of cholesterol, was injected into the gallbladder. At the end of twenty-four hours, 14.76 mg. of cholesterol was recovered from the concentrated contents, an increase of 9.07 mg., or 159 per cent.

*Dog IV.*—Twenty-five cubic centimeters of hepatic bile containing 3.35 mg. was injected into the gallbladder, and at the end of twenty-four hours 16.23 mg. was recovered, an increase of 12.88 mg., or 384 per cent. It may be interesting to note that the concentration of the A bile was quite low, being only 13.42 mg. per hundred cubic centimeters of bile.

13. Gardner, J. A., and Gainsborough, H.: Biochem. J. **21**:130, 1927.

*Dog V.*—Fifty cubic centimeters of hepatic bile containing 8.85 mg. of cholesterol (as estimated by the digitonin method) was injected into the gallbladder, and at the end of twenty-four hours the thick viscid bile, only about one fourth of its original quantity, was found to contain a total of 29.14 mg. of cholesterol by weight (digitonin). The increase was 20.29 mg., or 229 per cent.

*Dog VI.*—Twenty-five cubic centimeters of hepatic bile, containing 5.01 mg. of cholesterol, was injected. This bile was allowed to remain in the gallbladder for thirty-eight hours. At the end of this period, extremely thick precipitated bile was found to contain a total of 31.26 mg. of cholesterol, an increase of 26.25 mg., or 524 per cent.

*Dog VII.*—This animal was treated in a manner similar to the preceding ones with the exception that, for ten days previous to injection, 2 Gm. of cholesterol was added daily to the food in order to raise the cholesterol content of the blood. It has been shown that this content can be easily raised in rabbits by a high cholesterol diet.[4] There is some doubt, however, whether hypercholesterolemia can be produced in omnivorous animals. Lemoine and Gerard[14] and Rothschild and Rosenthal[15] have produced evidence that such hypercholesterolemia can occur. We have found it to be so in the case of dogs. Thus, on feeding two dogs, each weighing about 15 Kg., 1 Gm. of cholesterol daily in their food, the cholesterol content of the blood was approximately doubled in one week; in one case it rose from 77 to 155 mg. per hundred cubic centimeters of bile and in the other case from 99 to 208 mg. At the time of operation, 24 cc. of hepatic bile (derived from another dog with a biliary fistula), containing 6.45 mg. of cholesterol, was introduced into the emptied gallbladder. At the end of twenty-four hours, 35.85 mg. of cholesterol was recovered from the contents of the gallbladder, an increase of 29.4 mg., or 455 per cent. From this it would seem that raising the concentration of the cholesterol in the blood increased the amount of cholesterol entering the gallbladder.

*Dog VIII.*—In this animal, instead of the cholesterol of the blood being raised, the cholesterol of the hepatic bile was raised by adding an excess of sterilized cholesterol to a flask containing sterile hepatic bile and shaking this every few hours for two days. Prior to the operation, the bile was carefully decanted and filtered through several layers of sterile gauze to prevent any particles of cholesterol from being present in the solution. This procedure raised the A bile cholesterol to 47.24 mg. per hundred cubic centimeters of bile. Thirty cubic centimeters

14. Lemoine and Gerard: Bull. et mém. Soc. méd. de hôp. de Paris **33**:931, 1912.

15. Rothschild, M. A., and Rosenthal, N.: Am. J. M. Sc. **152**:394, 1916.

of this bile, containing 14.17 mg. of cholesterol, was introduced into the gallbladder. At the end of tweny-four hours, 27.85 mg. of cholesterol was recovered, an increase of 12.68 mg., or 89.5 per cent. This result indicates that raising the cholesterol of the bile without raising that of the blood decreases the amount of cholesterol passing into the bile of the gallbladder.

The majority of animals used for these experimental purposes are not listed, owing to the fact that at the end of twenty-four hours the wall of the gallbladder in some instances was found to be inflamed or gangrenous in histologic sections; in others, the results were discarded owing to interference with the blood supply or to the presence of aberrant hepatic ducts emptying into the gallbladder above the ligature, occluding the cystic duct. Only the few animals in which no inflammatory changes were seen in the histologic sections of the gallbladder wall are listed in this article.

TABLE 1.—*Results in Experiments on Eight Dogs*

| Dog | Duration, Hours | Amount, Cc. | | Mg. per 100 Cc. of Bile | | Amount, Mg. | | Change, Mg. | Percentage Change |
|---|---|---|---|---|---|---|---|---|---|
| | | A | B* | A | B* | A | B | | |
| I | 24 | 10 | 3 | 35.85 | 182 | 3.58 | 5.46 | 1.88 | 52.0 |
| II | 24 | 31 | 12 | 22.75 | 239 | 7.05 | 28.69 | 21.64 | 307.0 |
| III | 24 | 29 | 14 | 19.61 | 105 | 5.69 | 14.76 | 9.07 | 159.0 |
| IV | 24 | 25 | 11 | 13.42 | 147 | 3.35 | 16.23 | 12.88 | 384.0 |
| V | 24 | 50 | 15 | 17.7 | 194 | 8.85 | 29.14 | 20.29 | 229.0 |
| VI | 38 | 25 | 10 | 20.05 | 312 | 5.01 | 31.26 | 26.25 | 524.0 |
| VII | 24 | 24 | 10 | 26.85 | 358 | 6.45 | 35.85 | 29.40 | 455.0 |
| VIII | 22 | 30 | 15 | 47.24 | 185 | 14.17 | 27.85 | 12.68 | 89.5 |

* Approximate.

Table 1 gives the main points in the foregoing experiments.

From table 1 it would appear that cholesterol passes into the bile of the gallbladder from without. It will also be noticed that the cholesterol concentration of B bile is only approximate, as it is difficult to measure the B bile accurately after concentration and precipitation has taken place. Nevertheless, it is interesting to note that the milligrams of cholesterol per hundred cubic centimeters in the B bile approximately corresponds to the average blood cholesterol content of the dog. The following four experiments bring this point out more clearly, as in these animals accurate readings of the cholesterol content of the blood were taken during the twenty-four hours that the experiment was taking place. It has been found that the cholesterol content of the blood of these dogs may vary greatly within short intervals, so it was necessary to check the blood at the beginning and the end of the period of concentration of the A bile.

In dogs IX and X no effort was made to raise the cholesterol content of the blood, but cholesterol was added to the bile.

It was found that the solubility of cholesterol in bile depends on the percentage of bile salts present; thus, by adding increasing percentages of sodium taurocholate and excess cholesterol to different portions of a sample of bile, the amount of cholesterol dissolved was raised proportionately to the percentage of bile salts:

| | Cholesterol per 100 Cc. Bile |
|---|---|
| Bile + excess cholesterol | 23.0 mg. |
| Bile + 1% sodium taurocholate + cholesterol | 37.4 mg. |
| Bile + 2% sodium taurocholate + cholesterol | 60.6 mg. |
| Bile + 10% sodium taurocholate + cholesterol | 363.0 mg. |

*Dog IX.*—Our procedure was to add sterile sodium taurocholate and cholesterol to sterile hepatic bile, until a high concentration of cholesterol dissolved in the bile was reached; the excess cholesterol was removed by filtration, and the concentration of cholesterol was found to be 184.9 mg. per hundred cubic centimeters of bile. The cystic duct was occluded as before, and 25 cc. of this A bile, containing 36.98 mg. of cholesterol, was introduced into the emptied gallbladder. At the end of twenty-four hours the animal was killed, and approximately 8 cc. of concentrated bile containing 12.5 mg. of cholesterol was removed from the gallbladder, indicating a loss of 24.48 mg. of cholesterol during the period of twenty-four hours. In other words, 8 cc. of B bile contained 12.5 mg. of cholesterol, corresponding to a concentration of approximately 156 mg. of cholesterol per hundred cubic centimeters of bile. The cholesterol of the blood throughout this experiment averaged 170.5 mg. per hundred cubic centimeters of blood, indicating that the loss of cholesterol from the gallbladder resulted in a final concentration of the cholesterol of the bile corresponding to that of the blood stream.

*Dog X.*—As in dog IX, A bile with an artificially high concentration was used. Twenty-five cubic centimeters containing 34.37 mg of cholesterol (or 137.5 mg per hundred cubic centimeters of bile) was injected. At the end of twenty-four hours, approximately 8 cc. of bile was recovered, which contained only 14.6 mg. of cholesterol (an approximate concentration of 182.5 mg. per hundred cubic centimeters of bile). The average cholesterol content of the blood throughout the experiment was 163.5 mg. per hundred cubic centimeters of blood. In this case there was a loss of 19.77 mg. of cholesterol from the gallbladder, resulting in a final cholesterol concentration of the bile approximately equal to that of the blood.

*Dog XI.*—This animal was fed 2 Gm. of cholesterol daily, which was mixed with its food. On the sixth day, at the time of operation, the cholesterol content of the blood was 366 mg. per hundred cubic centimeters of blood. At the end of twenty-four hours, it was 296 mg., giving an average cholesterol content of the blood during the period of bile concentration of 330 mg. After the cystic duct was ligated and

the gallbladder emptied, 25 cc. of hepatic bile derived from a biliary fistula of another dog, containing 8.32 mg. of cholesterol (or 33.3 mg. per hundred cubic centimeters of bile), was introduced into the gallbladder. After twenty-four hours, approximately 8 cc. of bile remained, which on analysis contained 25 mg. of cholesterol (or 312.5 mg. per hundred cubic centimeters of bile). The increase by weight of cholesterol at the end of twenty-four hours was 16.68 mg. The final concentration of cholesterol in the bile was approximately 312.5 mg. per hundred cubic centimeters, whereas the average concentration of cholesterol in the blood stream throughout the experimental period was 330 mg. per hundred cubic centimeters of blood. These figures suggest a close relationship between the two.

*Dog XII.*—The cholesterol content of the blood of this dog was raised to an average of 425 mg. by the measures that were employed in dog XI. Fourteen cubic centimeters of hepatic bile, containing 3.78 mg. of cholesterol (or 27 mg. per hundred cubic centimeters of bile),

TABLE 2.—*Results of Experiments on Dogs IX, X, XI and XII*

| Dog | Duration, Hours | Amount, Cc. | | Mg. per 100 Cc. of Bile | | Amount, Mg. | | Change, Mg. | Percentage Change | Blood Cholesterol, Mg. % Average |
|---|---|---|---|---|---|---|---|---|---|---|
| | | A | B* | A | B* | A | B | | | |
| IX | 24 | 25 | 8 | 184.9 | 156.0 | 36.98 | 12.5 | −24.48 | — 66.0 | 170.5 |
| X | 24 | 25 | 8 | 137.5 | 192.5 | 34.37 | 14.6 | −19.77 | — 57.5 | 163.5 |
| XI | 24 | 25 | 8 | 33.3 | 312.5 | 8.32 | 25.0 | +16.68 | +200.0 | 330.0 |
| XII | 24 | 14 | 8 | 27.0 | 430.0 | 3.78 | 12.9 | + 9.12 | +241.0 | 425.0 |

* Approximate.

was introduced into the previously emptied gallbladder with the cystic duct occluded. At the end of twenty-four hours, approximately 3 cc. of bile was recovered, which contained 12.9 mg. of cholesterol (or 430 mg. per hundred cubic centimeters of bile). This shows an increase by weight in twenty-four hours of 9.12 mg. The cholesterol concentration of the bile was raised from 27 mg. to approximately 430 mg. per hundred cubic centimeters of bile, corresponding closely to the average cholesterol content of the blood of 425 mg. per hundred cubic centimeters of blood.

The results of the last four experiments are shown in table 2.

## COMMENT

From the foregoing experiments it would appear that in normal dogs cholesterol passes into the bile of the gallbladder from without; that is, the cholesterol is derived in some way from the wall of the gallbladder and deposited in the bile. It would also seem logical to assume that the cholesterol is brought to the gallbladder by the blood stream.

It should be remembered that in this work the technic that was employed corresponds closely to the normal physiologic process. Normally, the gallbladder receives dilute hepatic bile. While in contact with the mucosa of the gallbladder, this bile is rapidly concentrated, principally by the removal of water. Changes in the other constituents of the bile that take place within the gallbladder most likely occur concomitantly with the absorption of the water.

The experimental method imitates closely the physiologic process so far as normal hepatic bile is placed in contact with the mucosa of the gallbladder, and concentration of this bile is allowed to proceed for twenty-four hours. In other words, under controlled quantitative conditions the normal process is reproduced, aside from the fact that the gallbladder is not continually receiving hepatic bile owing to the artificial occlusion of the cystic duct.

Before proceeding further, it should be mentioned that two minor inaccuracies are present in this work. First, when the bile is withdrawn from the gallbladder in the initial procedure, a small quantity of this bile is undoubtedly left in the gallbladder, which is not included in the determination of A bile. Second, when the gallbladder is removed to recover the B bile, a certain amount is also left adherent to the mucosa, which, of course, does not enter into the determination of cholesterol. The latter error is unavoidable, as any washing or scraping of the mucosa would be apt to remove some of the delicate membrane, and the cholesterol content of the cells would then be included in the calculations. It is, however, self-evident that these are but slight errors, and in any case the one tends to offset the other.

A careful analysis of the figures in table 1, aside from indicating that cholesterol normally passes from the blood stream into the bile through the wall of the gallbladder, brought up a further interesting observation. The question arose as to whether cholesterol enters the bile of the gallbladder by active secretion or merely by ordinary filtration. If cholesterol enters the gallbladder by filtration, this process should be dependent on the ratio between the cholesterol content of the blood and the bile, and it may be seen from the figures already given that the amount of cholesterol entering the gallbladder apparently does depend (to at least a great extent) on this ratio. In dog VII, which was fed a high cholesterol diet to produce hypercholesteremia, a large increase of cholesterol is found in the bile at the end of twenty-four hours. If, on the other hand, the cholesterol content of the bile is high and that of the blood normal, there is a much smaller interchange of cholesterol at the end of a given time. This fact is well demonstrated in dog VIII, in which cholesterol was artificially added to the A bile, resulting in a very small increase at the end of twenty-four hours.

Further, as Illingworth [4] and Boyd have shown, if very high concentrations of cholesterol are introduced into the gallbladder (that is, higher than the blood) it tends to disappear from the bile of the gallbladder.

Thus in dogs II, III, IV and V, with an average A bile of 18.37 mg. per hundred cubic centimeters of bile, the average increase of cholesterol was 269 per cent at the end of twenty-four hours. In dog VII, which was fed a high cholesterol diet, the increase was 455 per cent. In dog VIII, on the contrary, in which the cholesterol of the blood was probably normal and in which the cholesterol of the hepatic bile was artificially raised, the actual increase in twenty-four hours was only 89.5 per cent. It therefore seemed logical to assume the possibility that if the cholesterol concentration of the bile should be higher than that of the blood, cholesterol would pass from the bile into the blood stream.

With these facts in view, it was decided to perform a series of experiments in which the cholesterol content of the blood was carefully estimated along with that of the bile. As may be seen by table 2, observations were made on two animals (dogs IX and X) in which the cholesterol content of the bile was artificially raised, with that of the blood remaining within normal limits; on two other animals (dogs XI and XII), the cholesterol content of the bile was more or less normal, but that of the blood was definitely raised by feeding a high cholesterol diet. In studying table 2, it is interesting to note that the B bile, irrespective of the concentration of the A bile, tends to approach an equilibrium with the cholesterol content of the blood. Two factors are involved in the production of this apparent equilibrium: (1) the reduction in volume of the A bile by the absorption of fluid; (2) the interchange of cholesterol between the bile and the blood stream, one way or another.

Dog XII, in which there was marked concentration, is a good example of both these points, the bile being concentrated from 14 to 3 cc. in twenty-four hours by the absorption of fluid. The 14 cc. of bile injected contained 3.78 mg. of cholesterol. If this amount of cholesterol remained constant and reduction in volume by removal of water were the only factor, the final 3 cc. of bile would have a cholesterol concentration of 127 mg. per hundred cubic centimeters of bile. Actually the final cholesterol concentration of the B bile was 430 mg. per hundred cubic centimeters of bile, which corresponds closely to that of the blood (425 mg. per hundred cubic centimeters of blood). We may therefore assume that this result was attained by the passage of cholesterol from the blood stream into the bile. In other words, although the absolute increase by weight of cholesterol in twenty-four hours was small (9.12 mg.), the combined effect of reduction in volume and of addition of cholesterol was to raise the cholesterol concentration of the B bile to a level with that of the blood.

In dogs IX and X, the equilibrium of cholesterol concentration between the blood and the bile was attained by the loss of cholesterol from the bile, compensating for the increased concentration due to the loss of fluid. Thus in dog IX the A bile concentration was 184.9 mg. per hundred cubic centimeters of bile (25 cc. containing 36.98 mg.), slightly higher than that of the blood (170.5 mg. per hundred cubic centimeters of blood). As before, if concentration were the only factor involved, the final 8 cc. of bile would show a concentration of 462.25 mg. of cholesterol per hundred cubic centimeters of bile. Actually, the final cholesterol concentration was only 156 mg. per hundred cubic centimeters of bile, approximating that of the blood. This result could be attained only by a loss of cholesterol from the bile of the gallbladder.

## CONCLUSIONS

1. In normal animals, with the cystic duct tied, when the cholesterol concentration of the bile is lower than that of the blood, cholesterol passes from the blood through the mucosa of the gallbladder into the bile.

2. When the cholesterol concentration of the bile is higher than that of the blood, cholesterol passes from the bile through the mucosa of the gallbladder into the blood stream.

3. The amount of cholesterol passing through the mucosa and the direction of its passage apparently depend on the blood-bile cholesterol ratio.

# EFFECTS ON COMPOSITION OF BLOOD OF PHYSIOLOGIC SOLUTION OF SODIUM CHLORIDE

## WHEN INTRODUCED BY INTRAPERITONEAL INJECTION AND BY STOMACH TUBE IN THE PRESENCE OF LOW BLOOD PRESSURE

J. W. BEARD, M.D.

HARWELL WILSON, M.D.

AND

ALFRED BLALOCK, M.D.

NASHVILLE, TENN.

This paper is a continuation of previously reported studies [1] of the effects of the administration of fluids to animals with low blood pressure. In the previous studies, fluid was administered intravenously and subcutaneously. The changes observed in the protein content of the blood were considered important. The present studies were carried out in order to determine the effects of physiologic solution of sodium chloride when introduced by intraperitoneal injection and by stomach tube into animals with low blood pressure. The subcutaneous injection of histamine and graded bleeding were the methods used to produce low blood pressure.

### METHODS

All of the experiments were carried out on dogs that were anesthetized with morphine. They gave no evidence of pain during the experiments. Shortly following the administration of the anesthetic, the blood volume was determined by

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From the Department of Surgery of Vanderbilt University.

1. Beard, J. W., and Blalock, Alfred: Intravenous Injections. A Study of the Composition of the Blood During Continuous Trauma to the Intestines When No Fluid is Injected and When Fluid is Injected Continuously, J. Clin. Investigation **11**:249 (March) 1932. Blalock, Alfred; Beard, J. W., and Thuss, Charles: Intravenous Injections. A Study of the Effects on the Composition of the Blood of the Injection of Various Fluids into Dogs with Normal and with Low Blood Pressures, J. Clin. Investigation **11**:267 (March) 1932. Beard, J. W.; Wilson, H.; Weinstein, B. M., and Blalock, A.: A Study of the Effects of Hemorrhage, Trauma, Histamine and Spinal Anesthesia on the Composition of the Blood When No Fluids Are Injected and When Fluids Are Introduced Intravenously, J. Clin. Investigation **11**:291 (March) 1932. Blalock, A., and Beard, J. W.: The Effects on the Composition of the Blood of the Subcutaneous Injection of Normal Salt Solution into Normal Dogs and into Dogs Subjected to Intestinal Trauma, Graded Hemorrhages and Histamine Injection, J. Clin. Investigation **11**:311 (March) 1932.

the dye method,[2] and samples of blood were withdrawn for the control determinations. Physiologic solution of sodium chloride was then introduced intraperitoneally or by stomach tube. When introduced into the peritoneal cavity, it was injected through a needle at a constant rate of 10 cc. per kilogram of body weight per hour for four hours. Samples of blood were removed for the analyses one, two and one-half and four hours following the beginning of the injection of fluid, and one and one-half and three hours following its completion. When given by stomach tube, one half of the amount, equal to 10 cc. per kilogram of body weight per hour for four hours, was given at the beginning of the experiment, and the remainder at the end of two hours. At the completion of the experiment, the amount of fluid remaining in the stomach or peritoneal cavity was measured. Following the withdrawal of a sample of blood, it was replaced by an equal amount obtained from another dog.

Experiments were first performed in which the effects of administration of fluids to normal dogs by the methods described were determined. In subsequent experiments the blood pressure was caused to decline by the withdrawal of blood from the femoral vein at intervals at the rate of 10 cc. per kilogram of body weight per hour for four hours. In the experiments in which the decline in pressure was produced by histamine, a solution of 0.1 per cent histamine phosphate was injected in sufficient amounts to maintain a depression of the blood pressure.

The hemoglobin was determined by the method described by Cohen and Smith.[3] Van Allen tubes were used for the hematocrit readings. The blood for protein analyses was allowed to clot, and the determinations were carried out on blood serum. The proteins were partitioned by the use of 22.2 per cent sodium sulphate, as recommended by Howe,[4] and the total protein content, the albumin content and the globulin content of each sample were determined by the Macro-Kjeldahl method, according to Gunning's modification.[5] On the basis of the original blood volume determined directly by the dye method, changes in blood volume were calculated from alterations in the hemoglobin. From the hematocrit estimations, the relative volumes of red blood cells and of plasma could be calculated. The absolute amount of protein in the circulation was calculated from protein per unit volume and plasma volume.

## RESULTS

I. *Effects on the Composition of the Blood of Continuous Injection of Physiologic Solution of Sodium Chloride into the Peritoneal Cavity.*—*A.* When the Blood Pressure Remained at a Normal Level: Three experiments were carried out, the results of which were entirely similar. There was a definite increase in plasma volume in each experiment, and a slight decrease in the amount of protein per unit volume. There was a small increase in the calculated absolute amount of protein in the entire

2. Rowntree, L. G., and Brown, G. E.: The Volume of the Blood and Plasma in Health and Disease, Mayo Clinic Monographs, Philadelphia, W. B. Saunders Company, 1929.

3. Cohen, B., and Smith, A. H.: The Colorimetric Determination of Hemoglobin, J. Biol. Chem. **39**:489, 1919.

4. Howe, P. E.: The Determination of the Proteins in Blood, J. Biol. Chem. **49**:109, 1921.

5. Gunning, J. W.: Ueber eine Modification der Kjeldahl-Methode, Ztschr. f. anal. Chem. **28**:188, 1889.

circulation. The changes in albumin and globulin were parallel to those in the total protein. In the three experiments, the average amount of fluid absorbed from the peritoneal cavity was 34 per cent of that injected. The results of these experiments are shown in table 1.

*B.* When the Blood Pressure Is Lowered by the Subcutaneous Administration of Histamine: The results of these experiments, of which there were three, differ considerably from those of the controls. There was a diminution in the amount of blood plasma in the circulation in all experiments. The percentage of protein per unit volume of plasma changed little. There was definite diminution in the absolute amount of plasma protein. The results of these experiments are given in table 2.

*C.* When the Blood Pressure Is Lowered by Hemorrhage: Two experiments were performed. The results obtained were essentially the same in each. The diminution of plasma volume was less than the amount present in the blood that was removed. There was a slight decrease in the percentage of protein. The absolute amount of protein in the circulation decreased, but if correction is made for the amount of protein removed in the blood a slight gain was shown. These figures are placed in brackets in the tables. An average of 24 per cent of the fluid placed in the peritoneal cavity during the two experiments was absorbed. The results of these experiments are shown in table 3.

II. *Effects on the Composition of the Blood of Introduction of Physiologic Solution of Sodium Chloride into the Stomach.—A.* When the Blood Pressure Remains at a Normal Level: The administration of physiologic solution of sodium chloride by stomach tube to dogs the blood pressure of which remained at essentially the normal level throughout the experiment caused little alteration in the percentage of protein of the blood serum. The results of one of the three experiments showed considerable loss of plasma during the experiment and a comparable loss of total protein. There was a slight increase in plasma volume in one experiment and a very slight diminution in the other. In the former, the absolute amount of protein in the circulation at the end of the experiment was almost exactly the same as at the control period, while in the latter, 2 Gm. of protein was lost during the seven hours. The results of these experiments are shown in table 4.

*B.* When the Blood Pressure Is Caused to Decline by the Subcutaneous Administration of Histamine: In both experiments of this series there was definite and considerable diminution in the plasma volume and comparable loss of protein. The protein per unit volume remained constant, and these results are essentially identical with those obtained when histamine is injected and no fluid is administered. Almost as much fluid

TABLE 1.—*Effects on the Composition of the Blood of the Continuous Injection of Physiologic Solution of Sodium Chloride into the Peritoneal Cavity*

| Experiment | Time from Beginning | Amount of Fluid Given | Total Protein | | Albumin | | Globulin | | Blood Volume from Hemoglobin and Hematocrit | | | Hematocrit | Hemoglobin | Mean Blood Pressure, Mm. Hg |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Blood, per Cent | Entire from Hemoglobin and Hematocrit | Blood, per Cent | Entire from Hemoglobin and Hematocrit | Blood, per Cent | Entire from Hemoglobin and Hematocrit | Red Blood Cells | Plasma | Whole | | | |
| T 154 | Control | 0 | 7.2 | 65.4 | 3.00 | 27.8 | 4.20 | 37.6 | (637) | (928) | (1,565) | 40.7 | 87.7 | 122 |
| 16.8 Kg. | 1 hr. | 168 | 7.2 | 67.2 | 3.08 | 29.4 | 4.12 | 37.8 | 637 | 955 | 1,592 | 40.0 | 86.2 | 105 |
| | 2 hr. 30 min. | 386 | 7.2 | 66.8 | 3.00 | 28.5 | 4.20 | 38.3 | 646 | 949 | 1,595 | 40.5 | 86.0 | 122 |
| | 4 hr. | 672 | 6.64 | 62.6 | 2.94 | 27.7 | 3.70 | 34.9 | 633 | 942 | 1,575 | 40.2 | 87.2 | 109 |
| | 5 hr. 30 min. | ... | 6.54 | 67.8 | 3.05 | 31.6 | 3.49 | 36.2 | 645 | 1,035 | 1,675 | 38.2 | 82.0 | 108 |
| | 7 hr. | ... | 6.57 | 67.0 | 2.83 | 28.9 | 3.74 | 38.1 | 645 | 1,020 | 1,665 | 38.8 | 82.4 | 101 |
| | Injected blood..... | | 8.38 | .... | 3.22 | .... | 5.16 | .... | ... | ..... | ..... | 33.5 | 63.6 | ... |
| T 155 | Control | 0 | 5.91 | 58.0 | 3.34 | 32.7 | 2.57 | 2.53 | (545) | (980) | (1,525) | 35.7 | 77.3 | 118 |
| 17.31 Kg. | 1 hr. | 173 | 5.78 | 56.8 | 3.25 | 32.0 | 2.53 | 2.48 | 532 | 983 | 1,515 | 35.2 | 77.7 | 111 |
| | 2 hr. 30 min. | 398 | 5.54 | 57.2 | 3.00 | 30.9 | 2.54 | 2.63 | 535 | 1,030 | 1,565 | 34.1 | 75.4 | 105 |
| | 4 hr. | 692 | 5.69 | 58.9 | 3.11 | 32.0 | 2.58 | 2.69 | 535 | 1,035 | 1,570 | 34.2 | 75.0 | 111 |
| | 5 hr. 30 min. | ... | 5.59 | 59.0 | 3.03 | 31.9 | 2.56 | 2.71 | 530 | 1,055 | 1,585 | 33.4 | 74.3 | 104 |
| | 7 hr. | ... | 5.50 | 60.2 | 2.94 | 32.2 | 2.56 | 2.80 | 521 | 1,094 | 1,615 | 32.3 | 73.0 | 104 |
| | Injected blood..... | | 7.05 | .... | 2.43 | .... | 4.62 | .... | ... | ..... | ..... | 29.0 | 64.1 | ... |
| T 156 | Control | 0 | 6.25 | 35.6 | .... | .... | .... | .... | (505) | (570) | (1,075) | 47.0 | 103.4 | 158 |
| 13.65 Kg. | 1 hr. | 136 | 6.19 | 36.9 | 3.99 | 23.8 | 2.20 | 13.1 | 516 | 596 | 1,112 | 46.4 | 100.0 | 132 |
| | 2 hr. 30 min. | 340 | 6.05 | 35.7 | 3.85 | 22.7 | 2.20 | 13.0 | 522 | 590 | 1,112 | 46.9 | 100.0 | 145 |
| | 4 hr. | 544 | 6.05 | 37.5 | 3.85 | 23.7 | 2.20 | 13.8 | 531 | 619 | 1,150 | 46.2 | 96.5 | 145 |
| | 5 hr. 30 min. | ... | 5.91 | 36.7 | .... | .... | .... | .... | 519 | 621 | 1,150 | 46.0 | 96.5 | 135 |
| | 7 hr. | ... | 5.82 | 38.3 | 3.56 | 23.5 | 2.26 | 14.8 | 542 | 658 | 1,200 | 45.2 | 92.6 | 125 |
| | Injected blood..... | | 7.37 | .... | 3.59 | .... | 3.78 | .... | ... | ..... | ..... | 36.9 | 62.5 | ... |

Protocols.—T 154: A total of 672 cc. of fluid was injected at the rate of 10 cc. per kilogram per hour into the peritoneal cavity. At the end of the experiment 475 cc. was recovered from the cavity, leaving 197 cc. that had been absorbed.

T 155: Fluid was injected into the peritoneal cavity continuously at the rate of 10 cc. per kilogram per hour, and a total of 692 cc. was injected. At the end of the experiment 370 cc. was recovered, and 322 cc. had been absorbed.

T 156: Fluid was injected into the peritoneal cavity continuously at the rate of 10 cc. per kilogram per hour, and a total of 544 cc. was given. At the end of the experiment 415 cc. was recovered, and 129 cc. had been absorbed.

TABLE 2.—*Effects of the Continuous Injection of Physiologic Solution of Sodium Chloride into the Peritoneal Cavity in the Presence of a Decline in Blood Pressure Produced by the Subcutaneous Injection of Histamine*

| Experiment | Time from Beginning | Amount of Fluid Given | Histamine, Mg. | Total Protein | | Albumin | | Globulin | | Blood Volume from Hemoglobin and Hematocrit | | | Hematocrit | Hemoglobin | Mean Blood Pressure, Mm. Hg |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Blood, per Cent | Entire from Hemoglobin and Hematocrit | Blood, per Cent | Entire from Hemoglobin and Hematocrit | Blood, per Cent | Entire from Hemoglobin and Hematocrit | Red Blood Cells | Plasma | Whole | | | |
| T 159 | Control | 0 | 10 | 5.30 | 28.2 | 2.83 | 15.0 | 2.47 | 13.2 | (302) | (532) | (834) | 36.2 | 82.4 | 108 |
| 9.5 Kg. | 1 hr. | 95 | 25 | 5.78 | 29.7 | 3.14 | 16.1 | 2.54 | 13.4 | 311 | 514 | 825 | 37.8 | 83.3 | 82 |
| | 2 hr. 30 min. | 238 | 40 | 5.78 | 29.5 | 3.03 | 15.5 | 2.75 | 14.0 | 315 | 510 | 825 | 38.2 | 83.3 | 65 |
| | 4 hr. | 380 | .. | 5.60 | 27.5 | 2.72 | 13.4 | 2.88 | 14.1 | 323 | 492 | 815 | 39.7 | 84.3 | 57 |
| | 5 hr. 30 min. | ... | .. | 5.55 | 27.5 | 2.66 | 13.2 | 2.89 | 14.3 | 317 | 495 | 812 | 38.0 | 84.7 | 57 |
| | 7 hr. | ... | .. | 4.88 | 24.8 | 2.43 | 12.4 | 2.45 | 12.4 | 317 | 508 | 825 | 38.5 | 83.3 | 74 |
| | Injected blood | | | 7.40 | .... | 2.32 | .... | 5.18 | .... | ... | ... | ... | 29.7 | 65.2 | ... |
| T 160 | Control | 0 | 10 | 4.71 | 33.0 | 2.49 | 17.4 | 2.22 | 15.6 | (503) | (700) | (1,203) | 41.8 | 90.9 | 100 |
| 12 Kg. | 1 hr. | 120 | .. | 5.05 | 28.7 | 2.23 | 12.7 | 2.82 | 16.0 | 512 | 568 | 1,080 | 47.4 | 101.3 | 63 |
| | 2 hr. 30 min. | 300 | 15 | 5.46 | 25.5 | 2.43 | 11.4 | 3.03 | 14.5 | 509 | 467 | 976 | 52.2 | 111.9 | 87 |
| | 4 hr. | 480 | 20 | 5.55 | 23.4 | 2.32 | 9.78 | 3.23 | 13.6 | 530 | 422 | 952 | 55.6 | 115.4 | 93 |
| | 5 hr. 30 min. | ... | .. | 5.68 | 23.3 | 2.60 | 10.7 | 3.08 | 12.7 | 525 | 411 | 936 | 56.0 | 117.1 | 116 |
| | 7 hr. | ... | .. | 5.68 | 25.2 | 2.55 | 11.3 | 3.13 | 13.9 | 526 | 444 | 970 | 54.2 | 112.7 | 100 |
| | Injected blood | | | 6.23 | .... | 3.66 | .... | 3.17 | .... | ... | ... | ... | 41.5 | 89.3 | ... |
| T 161 | Control | 0 | 10 | 6.23 | 36.0 | 3.62 | 20.9 | 2.61 | 15.8 | (390) | (578) | (968) | 40.4 | 92.0 | 120 |
| 10 Kg. | 1 hr. | 100 | 15 | 6.31 | 31.2 | 3.70 | 18.4 | 2.61 | 12.9 | 419 | 495 | 914 | 45.9 | 97.4 | 97 |
| | 2 hr. 30 min. | 250 | 20 | 6.31 | 29.3 | .... | .... | .... | .... | 405 | 465 | 870 | 46.2 | 101.3 | 84 |
| | 4 hr. | 400 | 45 | 6.50 | 28.2 | 3.90 | 16.9 | 2.60 | 11.3 | 408 | 434 | 842 | 48.5 | 105.6 | 66 |
| | 5 hr. 30 min. | ... | .. | 6.23 | 24.9 | 3.79 | 15.2 | 2.54 | 9.7 | 420 | 400 | 820 | 51.2 | 108.7 | 113 |
| | 7 hr. | ... | .. | 5.87 | 24.2 | 3.42 | 14.1 | 2.45 | 10.1 | 420 | 412 | 832 | 50.5 | 107.1 | 101 |
| | Injected blood | | | 4.37 | .... | 2.49 | .... | 1.88 | .... | ... | ... | ... | 33.4 | 75.0 | ... |

Protocols.—T 159: Following the control determination 10 mg. of histamine was administered subcutaneously, and the injection of fluid into the peritoneal cavity was begun at the same time. The total amount of fluid given was 380 cc., and at the end of the experiment 170 cc. was recovered from the peritoneum. The amount absorbed was, therefore, 210 cc. A total of 40 mg. of histamine was administered during the experiment.

T 160: Following the control determination 10 mg. of histamine was administered subcutaneously, and the injection of fluid into the peritoneal cavity was begun at the same time. The total amount of fluid given was 480 cc., and at the end of the experiment 525 cc. was recovered. Not only was no fluid absorbed, but there was a transudation of 45 cc. into the peritoneum. A total of 20 mg. of histamine was administered during the experiment.

T 161: Following the control determination 10 mg. of histamine was administered subcutaneously, and the injection of fluid into the peritoneal cavity was begun at the same time. The total amount of fluid given was 400 cc., and at the end of the experiment 205 cc. was recovered. The amount absorbed was, therefore, 295 cc. A total of 45 mg. of histamine was administered during the experiment.

TABLE 3.—*Effects of the Continuous Injection of Physiologic Solution of Sodium Chloride into the Peritoneal Cavity in the Presence of a Decline in Blood Pressure Produced by Graded Hemorrhage*

| Experiment | Time from Beginning | Amount of Fluid Given | Amount of Blood Withdrawn | Total Protein | | Albumin | | Globulin | | Blood Volume from Hemoglobin and Hematocrit | | | Hematocrit | Hemoglobin | Mean Blood Pressure, Mm. Hg |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Blood, per Cent | Entire from Hemoglobin and Hematocrit | Blood, per Cent | Entire from Hemoglobin and Hematocrit | Blood, per Cent | Entire from Hemoglobin and Hematocrit | Red Blood Cells | Plasma | Whole | | | |
| T 157 | Control | 0 | 166 | 7.14 | 92.4 | 2.83 | 36.6 | 4.31 | 55.8 | (555) | (1,295) | (1,850) | 30.0 | 69.4 | 107 |
| | | | | | (93.5) | | (34.4) | | (59.1) | | | | | | |
| 16.58 Kg. | 1 hr. | 166 | 414 | 7.04 | 85.2 | 2.57 | 31.1 | 4.47 | 54.1 | 500 | 1,210 | 1,710 | 29.4 | 68.2 | 95 |
| | | | | | (98.2) | | (36.6) | | (61.5) | | | | | | |
| | 2 hr. 30 min. | 415 | 662 | 6.73 | 77.6 | 2.51 | 28.9 | 4.22 | 48.7 | 441 | 1,154 | 1,595 | 27.7 | 62.5 | 103 |
| | | | | | (102.6) | | (39.5) | | (62.7) | | | | | | |
| | 4 hr. | 644 | ... | 6.45 | 70.0 | 2.51 | 27.2 | 3.94 | 42.8 | 370 | 1,085 | 1,455 | 25.3 | 57.9 | 76 |
| | | | | | (101.2) | | (38.1) | | (67.7) | | | | | | |
| | 5 hr. 30 min. | ... | ... | 6.32 | 68.6 | 2.38 | 25.8 | 3.94 | 42.8 | 370 | 1,085 | 1,455 | 25.4 | 57.9 | 64 |
| | | | | | (88.2) | | (33.4) | | (54.4) | | | | | | |
| | 7 hr. | ... | ... | 6.41 | 55.6 | 2.43 | 21.1 | 3.98 | 34.5 | 377 | 858 | 1,235 | 30.6 | 68.2 | 66 |
| T 158 | Control | 0 | 135 | 6.70 | 46.0 | 4.02 | 27.7 | 2.68 | 18.3 | (452) | (688) | (1,140) | 39.6 | 88.2 | 132 |
| | | | | | (43.6) | | (26.3) | | (17.2) | | | | | | |
| 13.5 Kg. | 1 hr. | 135 | 337 | 6.41 | 38.1 | 3.88 | 23.0 | 2.53 | 15.1 | 411 | 594 | 1,005 | 40.9 | 88.2 | 114 |
| | | | | | (45.9) | | (26.0) | | (19.8) | | | | | | |
| | 2 hr. 30 min. | 338 | 540 | 6.14 | 32.8 | 3.39 | 18.1 | 2.75 | 14.7 | 330 | 534 | 864 | 38.2 | 82.0 | 125 |
| | | | | | (47.3) | | (27.3) | | (19.8) | | | | | | |
| | 4 hr. | 540 | ... | 5.97 | 26.5 | 3.42 | 15.2 | 2.55 | 11.3 | 243 | 444 | 687 | 35.4 | 79.0 | 80 |
| | | | | | (47.2) | | (29.9) | | (19.1) | | | | | | |
| | 5 hr. 30 min. | ... | ... | 5.73 | 26.4 | 3.42 | 15.8 | 2.31 | 10.6 | 256 | 460 | 716 | 35.3 | 75.8 | 61 |
| | | | | | (47.5) | | (27.5) | | (19.8) | | | | | | |
| | 7 hr. | ... | ... | 5.64 | 26.7 | 3.25 | 15.4 | 2.39 | 11.3 | 243 | 473 | 716 | 34.0 | 75.8 | 54 |

Protocols.—T 157: Following the control determination 106 cc. of blood was withdrawn; at the end of one hour 248 cc. was withdrawn, and at the end of two and a half hours another 248 cc. was withdrawn. An equivalent amount of fluid was injected continuously intraperitoneally at the rate of 10 cc. per kilogram per hour, beginning simultaneously with the initial withdrawal of blood. A total of 644 cc. of fluid was given, and at the end of the experiment 420 cc. was recovered. The amount of fluid absorbed was 224 cc.

T 158: Following the control determination 135 cc. of blood was withdrawn; at the end of one hour 202 cc. was withdrawn, and at the end of two and a half hours another 248 cc. was withdrawn. An equivalent amount of fluid was injected continuously into the peritoneal cavity at the rate of 10 cc. per kilogram per hour beginning simultaneously with the initial withdrawal of blood. A total of 540 cc. of fluid was given, and at the end of the experiment 297 cc. was recovered. The amount of fluid absorbed was 243 cc.

TABLE 4.—*Effects on the Composition of the Blood of Introduction of Physiologic Solution of Sodium Chloride into the Stomach*

| Experiment | Time from Beginning | Amount of Fluid Given | Total Protein | | Albumin | | Globulin | | Blood Volume from Hemoglobin and Hematocrit | | | Hematocrit | Hemoglobin | Mean Blood Pressure, Mm. Hg |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Blood, per Cent | Entire from Hemoglobin and Hematocrit | Blood, per Cent | Entire from Hemoglobin and Hematocrit | Blood, per Cent | Entire from Hemoglobin and Hematocrit | Red Blood Cells | Plasma | Whole | | | |
| T 162 | Control | 0 | 6.47 | 57.4 | 2.89 | 25.6 | 3.58 | 31.8 | (573) | (887) | (1,460) | 39.3 | 88.2 | 138 |
| 16.75 Kg. | 1 hr. | 167 | 6.64 | 55.1 | 3.11 | 25.8 | 3.53 | 29.3 | 595 | 830 | 1,425 | 41.7 | 90.5 | 117 |
| | 2 hr. 30 min. | 412 | 6.82 | 58.0 | 3.23 | 27.4 | 3.59 | 30.6 | 590 | 850 | 1,440 | 41.1 | 89.3 | 135 |
| | 4 hr. | 668 | 6.55 | 52.4 | 3.31 | 26.5 | 3.24 | 25.9 | 570 | 800 | 1,370 | 41.6 | 93.8 | 135 |
| | 5 hr. 30 min. | ... | 6.47 | 59.5 | 3.06 | 28.1 | 2.41 | 31.4 | 595 | 920 | 1,515 | 40.3 | 85.2 | 108 |
| | 7 hr. | ... | 6.28 | 57.7 | 2.72 | 24.9 | 3.56 | 32.8 | 621 | 918 | 1,539 | 40.0 | 84.3 | 117 |
| | Injected blood..... | | 6.64 | .... | 2.21 | .... | 4.43 | .... | ... | ... | ..... | 29.3 | 66.3 | ... |
| T 163 | Control | 0 | 6.50 | 69.2 | .... | .... | .... | .... | (640) | (1,065) | (1,705) | 37.5 | 79.0 | 145 |
| 19.15 Kg. | 1 hr. | 191 | 5.82 | 53.1 | .... | .... | .... | .... | 618 | 912 | 1,530 | 40.3 | 88.2 | 125 |
| | 2 hr. 30 min. | 478 | 6.09 | 54.6 | .... | .... | .... | .... | 649 | 896 | 1,545 | 42.0 | 87.2 | 130 |
| | 4 hr. | 764 | 5.87 | 53.4 | .... | .... | .... | .... | 650 | 910 | 1,560 | 41.8 | 86.2 | 144 |
| | 5 hr. 30 min. | ... | 5.87 | 49.2 | .... | .... | .... | .... | 642 | 838 | 1,480 | 43.5 | 90.9 | 140 |
| | 7 hr. | ... | 6.12 | 47.1 | .... | .... | .... | .... | 650 | 770 | 1,420 | 45.8 | 94.9 | 135 |
| | Injected blood..... | | 5.41 | .... | .... | .... | .... | .... | ... | ... | ..... | 24.8 | 50.0 | ... |
| T 164 | Control | 0 | 6.17 | 38.8 | 3.85 | 24.1 | 2.32 | 14.7 | (497) | (628) | (1,125) | 44.2 | 95.5 | 132 |
| 12.9 Kg. | 1 hr. | 129 | 6.32 | 37.2 | 3.65 | 21.5 | 2.67 | 15.7 | 495 | 588 | 1,083 | 45.7 | 99.3 | 137 |
| | 2 hr. 30 min. | 323 | 6.43 | 37.0 | 3.62 | 20.7 | 2.81 | 16.3 | 503 | 572 | 1,075 | 46.8 | 100.0 | 133 |
| | 4 hr. | 516 | 6.28 | 34.7 | 3.77 | 20.8 | 2.51 | 13.9 | 508 | 552 | 1,060 | 47.9 | 101.3 | 126 |
| | 5 hr. 30 min. | ... | 6.37 | 35.3 | 3.60 | 20.0 | 2.77 | 15.3 | 505 | 555 | 1,060 | 47.7 | 101.3 | 106 |
| | 7 hr. | ... | 6.10 | 36.3 | 3.39 | 20.2 | 2.71 | 16.1 | 501 | 595 | 1,096 | 45.7 | 98.0 | 102 |
| | Injected blood..... | | 7.1 | .... | 3.14 | .... | 3.96 | .... | ... | ... | ..... | 32.0 | 79.0 | ... |

Protocols.—T 162: Fluid was run into the stomach continuously through a stomach tube, at the rate of 10 cc. per kilogram per hour. A total of 688 cc. was given. At the end of the experiment 110 cc. was found in the stomach. The dog vomited 70 cc. at the end of the second hour.

T 163: A total of 764 cc. of fluid was placed in the stomach during the experiment; one-half was run in at the beginning, and the other half at the end of two hours. At the end of the experiment 385 cc. of fluid remained in the stomach and 110 cc. was found in the peritoneal cavity. The dog did not vomit.

T 164: A total of 516 cc. of fluid was placed in the stomach during the experiment; one-half was run in at the beginning, and the other half at the end of two hours. At the end of the experiment 36 cc. of fluid remained in the stomach. The dog did not vomit.

TABLE 5.—*Effects of Introduction of Physiologic Solution of Sodium Chloride into the Stomach in the Presence of a Decline in Blood Pressure Produced by the Subcutaneous Injection of Histamine*

| Experiment | Time from Beginning | Amount of Fluid Given | Histamine, Mg. | Total Protein | | Albumin | | Globulin | | Blood Volume from Hemoglobin and Hematocrit | | | Hematocrit | Hemoglobin | Mean Blood Pressure, Mm. Hg |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Blood, per Cent | Entire from Hemoglobin and Hematocrit | Blood, per Cent | Entire from Hemoglobin and Hematocrit | Blood, per Cent | Entire from Hemoglobin and Hematocrit | Red Blood Cells | Plasma | Whole | | | |
| T 167 | Control | 0 | 0 | 7.32 | 61.4 | 4.21 | 35.2 | 3.11 | 26.2 | (675) | (838) | (1,513) | 44.7 | 102.7 | 135 |
| 15.6 Kg. | 1 hr. | 156 | 30 | 7.37 | 47.5 | 4.16 | 27.8 | 3.21 | 20.7 | 722 | 644 | 1,366 | 52.9 | 113.6 | 98 |
| | 2 hr. 30 min. | 390 | 65 | 7.63 | 44.5 | 4.21 | 24.6 | 3.42 | 19.9 | 742 | 584 | 1,326 | 56.0 | 117.1 | 85 |
| | 4 hr. | 624 | 125 | 7.19 | 42.9 | 4.04 | 24.1 | 3.15 | 18.8 | 753 | 597 | 1,350 | 55.8 | 115.4 | 84 |
| | 5 hr. 30 min. | ... | .. | 7.50 | 44.8 | 4.13 | 24.7 | 3.37 | 20.1 | 793 | 597 | 1.390 | 57.0 | 111.9 | 115 |
| | 7 hr. | ... | .. | 7.70 | 46.0 | 4.8 | 25.0 | 2.99 | 21.0 | 792 | 598 | 1,390 | 56.9 | 111.9 | 102 |
| | Injected blood..... | | | 6.46 | .... | 1.07 | .... | 5.40 | .... | ... | ... | ..... | 33.1 | 79.0 | ... |
| T 168 | Control | 0 | 0 | 6.13 | 44.0 | 4.75 | 34.1 | 1.38 | 9.9 | (573) | (717) | (1,290) | 44.5 | 91.0 | 119 |
| 17.7 Kg. | 1 hr. | 177 | 60 | 6.24 | 34.7 | 4.97 | 27.6 | 1.27 | 7.1 | 564 | 556 | 1,120 | 50.3 | 104.9 | 90 |
| | 2 hr. 30 min. | 443 | 80 | 5.92 | 35.9 | 4.52 | 27.4 | 1.40 | 8.5 | 554 | 606 | 1,160 | 47.8 | 101.3 | 65 |
| | 4 hr. | 698 | 120 | 6.06 | 36.1 | 4.52 | 26.9 | 1.44 | 9.2 | 564 | 596 | 1,160 | 48.6 | 101.3 | 83 |
| | 5 hr. 30 min. | ... | .. | 6.28 | 34.2 | 4.66 | 25.3 | 1.62 | 8.9 | 551 | 544 | 1,095 | 50.3 | 107.1 | 103 |
| | 7 hr. | ... | .. | 6.14 | 32.3 | 4.50 | 23.7 | 1.64 | 9.6 | 569 | 526 | 1,095 | 52.0 | 107.1 | 101 |
| | Injected blood..... | | | 6.96 | .... | 2.83 | .... | 4.13 | .... | ... | ... | ..... | 29.0 | 62.5 | ... |

Protocols.—T 167: A total of 624 cc. of fluid was placed in the stomach, one-half at the beginning of the experiment and the other half two hours later. Following the control determinations 10 mg. of histamine was administered, and enough thereafter to keep the blood pressure depressed. At the end of the experiment 550 cc. of fluid was found in the stomach. There was no vomiting.

T 168: A total of 700 cc. of fluid was placed in the stomach, one-half at the beginning of the experiment and the other half two hours later. Following the control determinations 10 mg. of histamine was administered, and enough thereafter to keep the blood pressure depressed. At the end of the experiment 550 cc. of fluid was found in the stomach. There was no vomiting.

TABLE 6.—*Effects of Introduction of Physiologic Solution of Sodium Chloride into the Stomach in the Presence of a Decline in Blood Pressure Produced by Graded Hemorrhage*

| Experiment | Time from Beginning | Amount of Fluid Given | Amount of Blood Withdrawn | Total Protein | | Albumin | | Globulin | | Blood Volume from Hemoglobin and Hematocrit | | | Hematocrit | Hemoglobin | Mean Blood Pressure, Mm. Hg |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Blood, per Cent | Entire from Hemoglobin and Hematocrit | Blood, per Cent | Entire from Hemoglobin and Hematocrit | Blood, per Cent | Entire from Hemoglobin and Hematocrit | Red Blood Cells | Plasma | Whole | | | |
| T 165 | Control | 0 | 127 | 5.91 | 46.1 | 3.70 | 28.8 | 2.21 | 17.3 | (456) | (780) | (1,236) | 36.9 | 79.0 | 115 |
| | | | | | (48.9) | | (30.4) | | (18.7) | | | | | | |
| 12.7 Kg. | 1 hr. | 127 | 317 | 5.54 | 44.2 | 3.42 | 27.3 | 2.12 | 16.9 | 392 | 798 | 1,190 | 32.6 | 73.5 | 98 |
| | | | | | (49.2) | | (30.1) | | (18.4) | | | | | | |
| | 2 hr. 30 min. | 318 | 417 | 5.58 | 36.9 | 3.48 | 23.0 | 2.00 | 13.9 | 350 | 660 | 1,010 | 34.6 | 72.8 | 88 |
| | | | | | (49.4) | | (29.5) | | (19.1) | | | | | | |
| | 4 hr. | 508 | ... | 5.80 | 33.3 | 3.50 | 20.1 | 2.30 | 13.2 | 309 | 574 | 883 | 35.0 | 75.0 | 62 |
| | | | | | (49.8) | | (29.7) | | (19.3) | | | | | | |
| | 5 hr. 15 min. | ... | ... | 5.59 | 33.7 | 3.37 | 20.3 | 2.22 | 13.4 | 311 | 603 | 914 | 34.0 | 72.5 | 29 |
| T 166 | Control | 0 | 121 | 7.14 | 42.7 | 4.67 | 28.0 | 2.47 | 14.7 | (539) | (599) | (1,138) | 47.4 | 105.6 | 132 |
| | | | | | (43.4) | | (26.3) | | (17.1) | | | | | | |
| 12.1 Kg. | 1 hr. | 121 | 276 | 7.68 | 38.9 | 4.61 | 23.3 | 3.07 | 15.7 | 496 | 506 | 1,002 | 49.5 | 107.1 | 133 |
| | | | | | (43.9) | | (26.6) | | (17.3) | | | | | | |
| | 2 hr. 30 min. | 303 | ... | 7.56 | 33.4 | 4.53 | 20.0 | 3.03 | 13.4 | 417 | 442 | 859 | 48.5 | 105.6 | 70 |
| | | | | | (42.4) | | (25.9) | | (16.5) | | | | | | |
| | 4 hr. | 484 | ... | 7.41 | 31.9 | 4.50 | 19.3 | 2.91 | 12.6 | 417 | 430 | 847 | 49.2 | 107.1 | 76 |

Protocols.—T 165: A total of 508 cc. of fluid was given into the stomach, 254 cc. at the beginning of the experiment and 254 cc. at the end of the second hour. Blood was withdrawn at intervals to equal 10 cc. per kilogram per hour. The third bleeding in the experiment was of 100 cc. which produced such a profound fall in pressure that the full amount could not be taken. Blood pressure declined gradually from this point, and the animal died at the end of five hours and forty-five minutes. The amount of fluid found in the stomach was 525 cc., while only 508 cc. had been injected.

T 166: In this experiment, the animal tolerated only two hemorrhages, 121 cc. at the beginning of the experiment and 155 cc. at the end of the second hour and a half. This dog died in four and a half hours. The total fluid placed in the stomach was 484 cc., and 425 cc. was recovered at the end of the experiment.

was found in the stomach of these dogs at the end of the experiment as was placed in them during the experimental period. The results of these experiments are given in table 5.

*C.* When the Blood Pressure Is Caused to Decline as the Result of Hemorrhage: It is perhaps significant that the animals in these two experiments neither tolerated the withdrawal of 10 cc. of blood per kilogram per hour for four hours nor lived through the usual seven hours of the experiments. The absolute amount of plasma protein in the circulation decreased, but this loss was accounted for by the protein in the withdrawn blood. The percentage of protein per unit volume of serum remained practically constant. The volume of blood plasma decreased rather markedly. Almost all of the fluid placed in the stomachs of these dogs was recovered at the end of the experiments. The results of these experiments are shown in table 6.

## COMMENT

The usual methods by which fluids are administered are intravenously, subcutaneously, intraperitoneally, by mouth and by rectum. In previous studies,[1] the effects on the composition of the blood of the administration of various fluids intravenously and of physiologic solution of sodium chloride subcutaneously to animals with a normal blood pressure and to those in which a decline in blood pressure had been produced by several means were determined. Particular emphasis has been placed on alterations in the percentage and absolute amounts of plasma protein, because protein maintains to a large degree the osmotic pressure of the blood stream. It has been shown previously[6] that the fluid that escapes from the blood stream as a result of trauma to the intestines, mild trauma to an extremity and burns has approximately the same protein content as the plasma of the blood stream. The introduction of physiologic solution of sodium chloride intravenously and of most of the other solutions frequently used in the treatment of shock caused little alteration in the composition of the blood when injected into dogs with normal blood pressures. When a decline in blood pressure was produced by hemorrhage and fluids were injected intravenously, the loss of protein was limited to that removed in the withdrawn blood. On the contrary, the intravenous injection of fluid into animals in which gross capillary injury had been inflicted by either mechanical or chemical means resulted in a loss of most of the fluid that was injected and in addition, in a decrease in the percentage of protein in the plasma remaining in the blood vessels. When salt solution was injected subcutaneously

6. Beard, J. W., and Blalock, A.: Experimental Shock. VIII. The Composition of the Fluid that Escapes from the Blood Stream After Mild Trauma to an Extremity, After Trauma to the Intestines and After Burns, Arch. Surg. **22**:617 (April) 1931.

into normal animals, there was little alteration in the composition of the blood. The subcutaneous injection of physiologic solution of sodium chloride into animals from which blood was removed was not associated with any additional loss of protein. In some instances there was a slight increase in the absolute amount of plasma protein if correction is made for the amount removed. When the subcutaneous injection of salt solution was accompanied by injury to large areas of capillaries, there was a large loss of protein from the circulation but that remaining was not diluted greatly, as was found in the experiments in which the fluid was given intravenously.

The results of the present experiments in which physiologic solution of sodium chloride was injected into the peritoneal cavity are similar to those that were obtained in the studies in which the fluid was injected subcutaneously. If any difference is present, it is in favor of the more rapid absorption by the blood stream of the fluid that was placed in the peritoneal cavity.

When, however, the salt solution was placed in the stomach, the results were similar to those obtained when no fluid was administered by any route. Studies of the composition of the blood indicated little if any absorption of the fluid that was placed in the stomach. It is possible that the morphine that was used as the anesthetic might have diminished the absorption of the fluid.

## SUMMARY

The effects on the composition of the blood of the introduction of physiologic solution of sodium chloride intraperitoneally and by stomach tube into normal dogs and into dogs in which a decline in blood pressure was produced by hemorrhage and by histamine have been determined. The studies included determinations of the arterial blood pressure, the percentage of hemoglobin, the concentration of the red blood cells, the volumes of whole blood, red blood cells and plasma, and the percentages of total protein, albumin and globulin in the blood serum.

The introduction of physiologic solution of sodium chloride into the peritoneal cavity of the normal dog was associated with an increase in the volume of plasma, a slight dilution of the protein of the plasma and a small increase in the absolute amount of plasma protein. When the blood pressure was caused to decline by giving histamine subcutaneously and salt solution was injected into the peritoneal cavity, there was a diminution in the volume of plasma and in the absolute amount of plasma protein. The percentage of protein per unit volume of plasma changed very little. The removal of blood and the introduction of salt solution intraperitoneally were associated with decreases in the plasma volume and in the absolute amount of plasma protein. However, the

losses of protein and plasma were less than the amounts removed in the blood. There was a slight dilution of the protein remaining in the circulation. The findings in these experiments in which the fluid was introduced intraperitoneally were similar to those obtained following the subcutaneous injection of solution.

The experiments in which physiologic solution of sodium chloride was introduced by stomach tube into normal dogs and into dogs with a low blood pressure showed no appreciable effects of the administration of fluid.

# ABSORPTION OF DEXTROSE FROM THE COLON

WALTER W. EBELING, M.D.
Hunter Fellow in Surgery
PHILADELPHIA

The ease with which fluids can be introduced through the rectum into the colon has resulted in the widespread use of this method for the administration of a variety of substances. There is undoubtedly a paucity of evidence from carefully controlled experiments on the ability of the colonic mucous membrane to absorb protein, fat or carbohydrate. It is well known that the rectal administration of ether results in general anesthesia. More recently the success with which narcosis may be produced by the rectal administration of sodium amytal and avertin proves that fairly complicated molecules may be absorbed by the mucosa of the large bowel. The sedative effect produced by the colonic administration of chloral hydrate or sodium bromide is a well established clinical phenomenon. The bromide ion, when administered rectally in sufficient amounts, can be recovered from the urine, the sweat and the lacrimal secretions. Recently, Cohn,[1] in this laboratory, found that iodine is readily absorbed from the colon.

The nutritive substance most often given either by rectal drip or by massive colonic instillation is dextrose. It supplies a variety of needs in the body economy. The evidence of its utilization when given into the large bowel has until recently been rather meager. Every textbook of therapeutics stresses the efficacy of administering dextrose by rectum to those patients requiring carbohydrates in instances in which the oral route cannot be used. No chapter on diabetes misses the opportunity of mentioning that dextrose may be administered by proctoclysis when necessary. In most surgical clinics the method has been used whenever the use of dextrose has been indicated and its administration by any other route has been inadvisable. The evidence on the total caloric value of the dextrose that can be absorbed from the large bowel is quite indefinite.

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From the Laboratory of Research Surgery and the Department of Surgery (Division C), University of Pennsylvania.

1. Cohn, B. N. E.: The Absorption of Compound Solution of Iodine from the Gastro-Intestinal Tract with Special Reference to Absorption of Free Iodine, Arch. Int. Med. **49**:950 (June) 1932.

Recently, experimental data published by McNealy and Willems [2] and by Scott and Zweighaft [3] question the ability of the large bowel to absorb dextrose. The experiments of McNealy and Willems were carried out on the colon of the dog. The large rectal ampulla was not utilized. Because of this, similar experiments have been performed, the entire colon and rectum being used—a method employed by Goldschmidt and Dayton [4] in their sodium chloride experiments. These studies have been extended to include a study of the degree to which the pancreatectomized dog with hyperglycemia and the hypoglycemic animal will absorb dextrose from the same portion of the alimentary tract. It is hoped that the present experiments will enhance our knowledge of the advisability and efficacy of administering dextrose by the rectal route as a therapeutic measure in the diabetic and nondiabetic patient. The step from the laboratory animal to the human patient is not so great but that some comparisons can be drawn.

## REVIEW OF THE LITERATURE

The early literature is replete with a variety of mixtures which were supposedly efficacious in maintaining life when given by the rectal route. How trustworthy these reports are cannot be stated.

Voit and Bauer [5] performed the first systematic research on the absorptive mechanism of the colon. Their experiments were performed with albumin, and they stated that the addition of sodium chloride assisted in the absorption of that substance. Czerny and Latschenberger [6] reported studies on two patients in whom the entire large intestine, or part of it, had been completely cut off from the small intestine. In these they obtained evidence which indicated that dextrose was absorbed. Deucher [7] reported that he gave five enemas to a patient during nineteen hours, each containing 40 Gm. of dextrose. One hundred and fifty-four grams of dextrose was absorbed, constituting 77 per cent of the amount introduced. Reach,[8] experimenting with normal men, found that there was a slight rise in the respiratory quotient, which corresponded to a rise in the peripheral blood sugar after the rectal administration of dextrose. He assumed that there was

2. McNealy, R. W., and Willems, J. D.: Surg., Gynec. & Obst. **49**:794, 1929.

3. Scott, E. L., and Zweighaft, J. F. B.: Blood Sugar in Man Following the Rectal Administration of Dextrose, Arch. Int. Med. **49**:221 (Feb.) 1932.

4. Goldschmidt, S., and Dayton, A. B.: Am. J. Physiol. **48**:419, 1919. Goldschmidt, S.: Physiol. Rev. **1**:421, 1921.

5. Voit, C., and Bauer, J.: Ztschr. f. Biol. **5**:537, 1869.

6. Czerny, von V., and Latschenberger, J.: Virchows Arch. f. path. Anat. **59**: 161, 1874.

7. Deucher, P.: Deutsches Arch. f. klin. Med. **58**:210, 1897.

8. Reach, F.: Arch. f. exper. Path. u. Pharmakol. **47**:231, 1902.

some absorption of dextrose. Zehmisch,[9] working with human beings, gave 152 Gm. of dextrose by rectum and lost 103 Gm. (67.5 per cent), supposedly by absorption. Arnheim[10] gave 50 Gm. of dextrose by bowel to diabetic persons. He was able to recover only 3 Gm. of dextrose after a period of five hours. He did not believe that bacterial action could account for the dextrose that had disappeared. Boyd and Robertson[11] fed seven women on nutrient enemas for from six to seven days. Each day the bowel was washed out and the contents analyzed. Urinary nitrogen was used as a gage of the absorption of nitrogenous substances. They reported that in two cases 100 per cent of the introduced dextrose was absorbed. They lost as much as 61.8 and 81 Gm. of dextrose during twenty-four hours, but recovered the bulk of the protein in the rectal washings. After having incubated dextrose solutions which were contaminated with colon bacilli, they concluded that the dextrose lost by bacterial action was insignificant. They were not able to produce dextrosuria with the amounts they administered. Halasz,[12] working with patients, placed clysters in the large bowel and, in from five to six hours, found that from 50 to 200 Gm. of the dextrose had disappeared. He accounted for only from 0.5 to 1 per cent of the dextrose as lost by bacterial action. Mutch and Ryffell[13] gave four enemas to each of several patients during a twenty-four hour period. Each enema consisted of 450 cc. of 6 per cent dextrose. When the nutrient enemas were well tolerated, they increased the dextrose to 60 Gm. to the pint of solution. Using a "washout" method of experimentation, they concluded that dextrose could be satisfactorily administered by this route to a maximum of 700 calories per day. Hari and Halasz,[14] working with dogs, placed a ligature around the ileocecal valve and, after the introduction of dextrose solution into the rectum, found that the respiratory quotient was nearly always increased. They reported that they were able to produce actual dextrosuria after the rectal administration of dextrose to their animals. Tallerman[15] gave dextrose enemas to seven normal persons and to one patient with functional vomiting. The solution consisted of 60 Gm. of dextrose in 180 cc. of physiologic solution of sodium chloride, or a 33 per cent dextrose solution. He concluded that absorption took place uniformly, the maximum rise in blood sugar occurring in about one

9. Zehmisch, F.: Ausnutzung von Nährklystieren, Halle, C. Nietschmann, 1903.

10. Arnheim, J.: Ztschr. f. diätet. u. phys. Therap. **8**:75, 1905.

11. Boyd, F. D., and Robertson, T.: Scottish M. & S. J. **18**:193, 1906.

12. Halasz, A. V.: Deutsches Arch. f. klin. Med. **98**:433, 1910.

13. Mutch, N., and Ryffell, J. H.: Guy's Hosp. Rep. **66**:223, 1912.

14. Hari, P., and Halasz, A. V.: Biochem. Ztschr. **88**:337, 1918.

15. Tallerman, K. H.: Quart. J. Med. **13**:356, 1919-1920.

hour and twenty minutes with an average rise of 30 mg. per hundred cubic centimeters of blood. Varela and Rubino [16] stressed the necessity of exposing the dextrose solution to the rich venous plexus of the rectal ampulla. They placed 40 per cent dextrose solutions in the rectums of patients and tested the peripheral blood and urine for dextrose. They found that minute amounts were absorbed shortly after the dextrose was introduced, but that soon the colon became irritated and expelled the enema. Carpenter,[17] in two experiments on human beings, gave 30 Gm. of dextrose in 500 cc. of physiologic solution of sodium chloride. Within two or three hours after the injection, the respiratory quotient changed from 0.02 to 0.05. He found that 17.5 Gm. of dextrose was absorbed in one instance and, in the other, 26.3 Gm. Similarly, five hours after the administration of 60 Gm. of dextrose, he found that 34.6 Gm. had apparently been absorbed. The quantitative results were based on the "washout" method, using more than one lavage.

Bingel [18] investigated the absorption of dextrose in diabetic patients. He concluded that only small amounts of dextrose were absorbed. One hour after having placed 35 Gm. of dextrose in the bowel, 31 Gm. was recovered in the stool. Bingel incubated fecal material with added dextrose, and claimed that the dextrose lost was almost as great as that supposed to have been absorbed.

Franke and Wagner [19] gave concentrated enemas to dogs. They used 25 Gm. of dextrose in a 50 per cent solution. They determined the peripheral blood sugar at fifteen, thirty, forty-five and sixty minute intervals, and found the highest rise of blood sugar to be 20 mg. per hundred cubic centimeters. They concluded that dextrose enemas had little, if any, effect on the peripheral blood sugar. Levi [20] gave dextrose to fasting normal, diabetic and postoperative patients. He used 500 cc. of from 10 to 16 per cent dextrose solutions and found that patients varied as to their reaction, but, in general, took up only slight amounts of the dextrose.

McNealy and Willems, in 1929, working with isolated loops of the large and small bowel of the dog, gave this problem renewed interest. They introduced known amounts of dextrose into the colon or ileum and studied the changes quantitatively. They also studied the ileal, colic and peripheral venous blood sugar during the experiment. They used a 5 per cent dextrose solution and found that from 0.3 per cent

16. Varela and Rubino: Med. Klin. **18**:831, 1922.

17. Carpenter, T. M.: Human Metabolism with Enemata of Alcohol, Dextrose, and Levulose, publ. 369, Washington, D. C., Carnegie Institution, 1925.

18. Bingel, A.: Therap. d. Gegenw. **46**:436, 1905.

19. Franke, W., and Wagner, R. J.: J. Metab. Research **6**:375, 1924.

20. Levi, D.: Brit. J. Surg. **15**:282, 1927.

to as much as 2.6 per cent of the dextrose was lost from the large bowel, with a corresponding loss of from 23.3 to 59 per cent from the ileum over the same time interval. They found that the colic venous blood sugar fell, while the blood sugar from the ileal vein in the ileal experiments rose. They concluded that a 5 per cent dextrose solution was of little or no nutritional value when administered rectally. They suspected the presence of an incompetent ileocecal valve as the basis for some of the experimental and clinical success reported in the literature. Later,[21] they reported the effect of sodium chloride on dextrose absorption from the colon and found that, although the percentage of absorption was slightly greater, it was not sufficient to be of practical importance.

Pressman [22] gave 33 per cent dextrose solutions by rectum and by mouth to human beings and observed the blood sugar curves for a period of four hours. He found that the peripheral blood sugar level fell after the introduction of dextrose into the rectum without any significant preliminary rise. He recovered an average of 24 per cent from the colon after four hours. He stated that 90 per cent of the dextrose was destroyed by incubation with feces in seven hours. De Takáts,[23] in 1931, gave 1,000 cc. of 5 per cent dextrose to patients under the skin, by mouth and by bowel. The blood sugar level rose after introduction of dextrose under the skin and by mouth. When the dextrose was given by rectum, the blood sugar fell during a period of two hours. He noted that no dependence could be placed on the amount absorbed by rectum, and that insulin reactions occurred when this method of entry was depended on in the diabetic person.

Scott and Zweighaft, in experiments on medical students, investigated the blood sugar changes following the rectal administration of dextrose. They found no rise in the peripheral blood sugar after the administration of 180 cc. of a 15 or 30 per cent solution of dextrose. They also found that, after the rectal introduction of 200 cc. of a 10 per cent dextrose solution, the blood sugar level fell about 10 mg. per hundred cubic centimeters, while after the administration of 400 cc. of a 10 per cent dextrose solution the fall was about 7.5 mg. per hundred cubic centimeters. They concluded that the fall in blood sugar was due to pancreatic action or chance variation. They were able to recover from 25 to 50 per cent of the dextrose they had administered.

Since this paper went to press, Perusse [23a] has published data that led him to make the following statement: "We can then perhaps come

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21. McNealy, R. W., and Willems, J. D.: The Absorption of Dextrose from the Colon: II. A Study of the Effects of Chemical Excitants and of Stimulants of Dextrose Enema, Arch. Surg. **22**:649 (April) 1931.

22. Pressman, J. J.: Am. J. M. Sc. **179**:520, 1930.

23. de Takáts, G.: Am. J. Surg. **11**:39, 1931.

23a. Perusse: Surg., Gynec. & Obst. **54**:770, 1932.

to the tentative conclusion that 1 per cent glucose solution is the ideal for restoring water balance and for supplying some degree of nutrient."

## COMMENTS ON PREVIOUS EXPERIMENTAL AND CLINICAL OBSERVATIONS

There are certain obvious objections to the methods used by some of the investigators whose work has been cited. The "washout" method has been widely criticized on the ground that it fails to consider adequately: (1) bacterial action on the introduced dextrose; (2) the fact that reverse peristalsis may carry the solution beyond the reach of recovery, or even through an incompetent ileocecal valve into the ileum where absorption may occur.

Recent investigations of the responsibility of bacterial action for the loss of some of the dextrose from the large bowel give contradictory results. Cori,[24] in 1925, incubated the small intestines with known contained quantities of dextrose for from three to five hours at 37 C., and he concluded that the amount of dextrose lost in this part of the bowel by bacterial action was so small that it was negligible. Bingel [18] incubated fecal material with dextrose and claimed that the quantity lost through bacterial action was equal to the amount supposed to have been absorbed. Pressman [22] incubated dextrose and feces for seven hours. He found that nearly 90 per cent of the dextrose had been destroyed. McNealy and Willems [2] avoided the question of loss of dextrose in this manner by using a short period of experimentation.

Experimental and clinical data demonstrate that the incompetency of the ileocecal valve may play a large part in those instances in which absorption has been demonstrated. Cannon [25] found that large injections into the colon go into the small intestine by means of antiperistalsis. Case [26] stated that the true cause of insufficiency of the ileocecal valve is overdistention of the right half of the colon. He found insufficiency in one sixth of 1,500 cases of constipation, observed roentgenologically. A personal communication from Pendergrass [27] supports this observation.

Other methods for the solution of the problem of dextrose absorption have been offered. Salvesen [28] reported a fall in the inorganic phosphates following injection of dextrose into the blood stream. Bollinger and Hartman [29] and Harrop and Benedict [30] have also

24. Cori, C. F.: J. Biol. Chem. **66**:691, 1925.
25. Cannon, W. B.: Am. J. Physiol. **6**:251, 1902.
26. Case, J. T.: Arch. Roentgen Ray **19**:375, 1915.
27. Pendergrass, E. P.: Personal communication.
28. Salvesen, H. A.: J. Biol. Chem. **56**:443, 1923.
29. Bollinger, A., and Hartman, F. W.: J. Biol. Chem. **64**:91, 1925.
30. Harrop, G. A., Jr., and Benedict, E. M.: J. Biol. Chem. **59**:683, 1924.

reported changes in the inorganic phosphates of the serum after injections of dextrose. I am not aware that the level of blood inorganic phosphates has been used as a measure of the absorption of dextrose from the colon. The use of the respiratory quotient in this type of experiment is open to some question unless the results are striking. Brodie,[31] in 1910, demonstrated that the introduction of distilled water into the bowel might cause increased oxygen consumption.

Diabetic patients show a marked variation in the readiness with which the liver glycogen may be mobilized in response to nervous stimulation and to mechanical pressure changes in the intestinal tract. This factor, as brought out by Smith[32] in 1930, may influence the respiratory quotient. Furthermore, the sensitive patient may show a slight rise in the sugar in the blood from the mere insertion of a rectal tube with a later and more marked rise in the blood sugar if the amount of solution introduced into the rectum is sufficient to cause marked distention of the intestine. This reversal of glycogen synthesis may be responsible for the increase in the respiratory quotient noted.

So far as I have been able to ascertain from a careful search of the literature, no one whose experiments have been controlled has found the marked alterations of the peripheral venous blood sugar after the rectal administration of dextrose which are encountered when dextrose is given by mouth.

Cori,[33] after investigation of the alimentary absorption of dextrose, has concluded recently that the peripheral blood sugar curve is not a measure of intestinal absorption. Magee and Reid,[34] on the contrary, have concluded that the dextrose curve is an index of intestinal absorption. They compared the portal and systemic blood during the absorption of dextrose from the intestine and found that the preabsorption values were practically always identical, but that about three minutes after the ingestion of the solution the portal blood sugar had risen about 20 mg. higher than the systemic blood sugar. These relative positions were approximately maintained until the end of the experiment. They assumed that the difference between the curves could be interpreted to represent the balance between the effects of hepatic function and of tissue metabolism on the blood sugar, and the systemic (venous) curve afforded as good an index of the rate of absorption as the portal curve.

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31. Brodie, T. G.; Cullis, W. C., and Halliburton, W. D.: J. Physiol. **40**:173, 1910.

32. Smith, B.: California & West. Med. **33**:857, 1930.

33. Cori, C.: Physiol. Rev. **11**:143, 1931.

34. Magee, H. E., and Reid, E.: J. Physiol. **73**:163, 1931.

The strength of the solution used in the bowel in attempting to demonstrate absorption has varied considerably. Goldschmidt [35] observed that the absorption from the entire length of the intestinal tract, so far as sodium chloride was concerned, involved a similar mechanism, and that the mechanism could be qualitatively explained by the known laws of osmosis. Theoretically, a 4.9 per cent dextrose solution has the same osmotic tension as physiologic solution of sodium chloride. Hausman [36] demonstrated that hypertonic solutions may produce undesirable results. He caused death in rats through the withdrawal of large quantities of water into the peritoneal cavity by means of a 50 per cent solution of dextrose. Certain of the variations in the results of different investigators may be explained by the difference in the concentrations of dextrose which were used.

In consideration of the literature and experimental data covered in this résumé, an experiment on the problem of dextrose absorption from the intestinal tract in the normal, the pancreatectomized and the insulinized animal was outlined which:

(1) Eliminated the ileum and isolated the colon and rectum.

(2) Considered the absorption of isotonic as well as hypertonic dextrose solution in the normal dog and isotonic dextrose solutions in the pancreatectomized, hyperglycemic, and in the insulinized, hypoglycemic, dog.

(3) Eliminated the possibility of intestinal putrefaction or bacterial action as a great factor in the loss of dextrose by careful cleansing of the bowel and by limiting the time of the experiment.

(4) Measured the absorption of dextrose in three ways simultaneously:
   (*a*) recovery and washings
   (*b*) peripheral blood sugar studies
   (*c*) colonic blood sugar studies

(5) Was controlled in the following ways:
   (*a*) Similar experiments were made with loops of ileum of equal length where dextrose absorption is known to take place.
   (*b*) An inert substance (paraffin oil) was introduced into the colon and rectum to control possible alterations in the blood sugar due to mere filling of the bowel.
   (*c*) Loss of dextrose through bacterial action and mere handling was determined by the incubation of a known dextrose solution within a colon and rectum removed from a freshly killed animal, washed and prepared in a similar manner over the same time period.
   (*d*) The possible presence of large amounts of nondextrose copper-reducing substances was eliminated by the introduction of distilled water into the colon and rectum under like methods and titration of the recovered solution by the same method used in the colonic dextrose determinations.

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35. Goldschmidt, S.: Physiol. Rev. **1**:421, 1921.

36. Hausman, W.: Wien. klin. Wchnschr. **38**:332, 1925.

## EXPERIMENTAL METHOD

In the experimental work twenty-four dogs were used. They were of mongrel breeds, and weighed from 7 to 32 Kg. The average weight was about 10 Kg. All dogs received their last feedings at 4 o'clock on the day before the experiment. Sodium amytal (sodium iso-amyl ethyl barbiturate) anesthesia was employed, 50 mg. per kilogram of body weight being introduced intraperitoneally. Nearly all the dogs went to sleep without excitement and slept quietly throughout the entire experiment with deep, slow respiration, although there was an occasional exception to this.

The abdomen was opened, and the appendix with the adjacent ileum was mobilized and brought into the wound. Two ligatures were passed around the ileum at its cecal junction and tightly tied. The tip of the appendix was then removed, and a glass cannula with an attached fenestrated rubber tube was inserted through the appendix into the cecum. The fenestrated rubber tube prevents collapse of the bowel for a distance of about 3 inches. Two ligatures were used to fasten the stump of the appendix about the cannula. Another rubber tube was attached to the end of the cannula which projected from the appendical stump.

The colon was washed out throughly by running warm tap water into the appendical cannula by means of a funnel. When the water coming from the rectum was clear, a tube similar to that in the cecum was inserted into the rectum. Leakage around the tube was prevented by means of a purse-string suture placed in the rectal sphincter. The colon was again flushed with warm tap water. Any fluid remaining was then forced out by gently passing air through the appendical cannula and elevating the head of the table. The operative procedure rarely took longer than thirty minutes.

Specimens of blood were taken from one of the veins draining the colic blood and from the exposed femoral vein. After the colon was carefully evacuated so that the bowel was collapsed, the rectal tube was clamped, and a dextrose solution of desired strength and known amount was allowed to run into the system at a pressure not exceeding 150 mm. of the solution. When the bowel appeared to be full, but not unduly distended, the appendical clamp was closed. The quantity of solution introduced varied with the size of the animal, 158 and 238 cc. being the lowest and highest amounts used. All solutions were warmed to 38.5 C. before being placed in the bowel. The abdominal incision was then closed, the appendical cannula extending through the closed wound.

Specimens of blood from the femoral vein were taken at half hour intervals. At the end of two hours the last specimen was taken, the abdomen again opened, and a specimen withdrawn from the colic vein. Difficulty in the control of hemorrhage from the colic vessel prevented the withdrawal of blood at more frequent intervals. Following the collection of the blood specimens, the solution remaining within the bowel was forced through the rectal cannula into a beaker by means of air. The head of the table was again elevated in order to facilitate the recovery of fluid. The bowel was flushed with 250 cc. of distilled water, this solution also being forced out into a second beaker by means of air and elevation of the head of the table. It is of interest that, of the 250 cc. of wash water introduced at this time, it was not unusual to recover all 250 cc. Occasionally a few cubic centimeters was lost and, at other times, 2 or 3 cc. more was recovered. A series of experiments on the ability to recover known amounts of fluid by this method showed that the error averaged 2 per cent ($\pm$ 2 per cent).

At the close of the experiment the animal was killed, and a section of the colon was removed for microscopic examination.

In the experiments on the ileum, loops approximately equal in length to the colon were isolated near the terminal portion. The loops were cannulated with Paul tubes with attached fenestrated rubber tubes. Blood specimens were withdrawn from the large ileal vein opposite the selected loop.

The pancreatectomies were performed under sodium amytal anesthesia. The operations were done with aseptic technic, and the pancreas was removed with no injury to the duodenal vessels. A specimen of the blood sugar during fasting was taken before pancreatectomy, the morning following and each morning thereafter. When the blood sugar level during fasting indicated marked hyperglycemia, the absorption experiments were performed. Blood sugar levels prior to the dextrose absorption experiments varied from 225 to 325 mg. per hundred cubic centimeters. The interval between pancreatectomy and the dextrose absorption experiment varied from two to four days.

For the hypoglycemic animals, the following method was used. Specimens of blood from the peripheral and colic veins were taken, following which 10 units of insulin per kilogram of body weight was given subcutaneously. After a lapse of one-half hour, blood was again taken from the colic and femoral veins and the dextrose solution introduced, after which the absorption experiment was carried out in the usual manner.

All dextrose solutions were prepared from Bacto-dextrose. The dextrose in each instance was weighed and diluted to volume, after which the solution was titrated for the concentration of dextrose present. The latter figure is used throughout in the final calculations.

The effect on the blood sugar level of the introduction of an inert substance (paraffin oil) into the colon was observed in several experiments. These experiments were performed in the same manner as the usual absorption experiment, except that warmed paraffin oil was allowed to flow into the colon instead of the usual dextrose solution.

The effect of bacterial action and handling on a known amount of dextrose solution in a completely excised colon from a freshly killed animal was tested. The excised colon was washed and prepared in a manner similar to that used in the intact animal. Seventy-five cubic centimeters of an approximately 5 per cent dextrose solution containing 3.31 Gm. of dextrose was placed within the bowel, and the entire preparation placed in a beaker and incubated at 37.5 C. for two hours. At the end of that time the solution was recovered. The bowel and beaker were washed with 250 cc. of distilled water, and the dextrose content of each solution was determined.

All solutions recovered, as well as washings, were quantitatively analyzed by the Benedict method [37] immediately after completion of the experiment in order to eliminate the possibility of loss of dextrose through standing and bacterial action. Some of the solutions, especially when hypertonic dextrose was used, contained mucus, so that it was necessary to filter or centrifugate them before titration.

Because of the fact that the Benedict method is based on the reduction of copper, it was necessary to determine the possible presence of nondextrose copper-reducing substances in the solutions exposed to the intestinal mucous membrane. For this experiment the colon of an anesthetized animal was prepared in the usual manner, and 200 cc. of distilled water was introduced. After the lapse of two hours, the solution was withdrawn in the usual way and titrated by the Benedict method.[37]

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37. Benedict, S. R.: The Detection and Estimation of Glucose in the Urine, J. A. M. A. **57**:1193 (Oct. 7) 1911.

All blood sugar determinations were made in duplicate by the Hagedorn and Jensen micromethod.[38] In several of the earlier experiments, Dr. Leon Jonas made simultaneous determinations by the Folin-Wu method. Except for the slightly lower level of the former determinations, the results were approximately the same.

## RESULTS

*The Absorption of a 5 Per Cent Dextrose Solution from the Ileum.*—In tables 1 and 1*a* the results from three experiments are given. In every experiment water and dextrose were absorbed, and the concentration of the dextrose in the loop fell. There is a close relationship

TABLE 1.—*Five Per Cent Dextrose Solution in Ileum of Normal Dog*

| Dog No. | Weight, Kg. | Solution Introduced, Cc. | Percentage Concentration In | Solution Out, Cc. | Percentage Concentration Out | Fluid Volume Change, Cc. | Percentage | Dextrose Introduced, Gm. | Dextrose Out, Gm. | Dextrose Recovered, in Washing, Gm. | Total Dextrose Out, Gm. | Dextrose Lost, Gm. | Percentage Dextrose Recovered | Percentage Dextrose Lost |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 815 | 11.2 | 240 | 4.1 | 214 | 3.6 | —26 | —10.4 | 9.84 | 7.70 | 0.41 | 8.11 | 1.73 | 82.4 | 17.6 |
| 1067 | 13.3 | 184 | 4.8 | 129 | 3.4 | —55 | —29.8 | 8.83 | 4.39 | 0.39 | 4.78 | 4.05 | 54.2 | 45.8 |
| 1068 | 7.8 | 158 | 4.5 | 138 | 3.95 | —20 | —12.6 | 7.11 | 5.45 | 0.35 | 5.80 | 1.31 | 81.6 | 18.4 |
| Mean..... | | 194 | | 160 | | —34 | —17.6 | 8.59 | | | 6.23 | 2.36 | 72.7 | 27.3 |

TABLE 1*a*.—*Peripheral and Ileal Venous Sugars Following Introduction of 5 Per Cent Dextrose Solution in Ileum of Normal Dog*

| | Peripheral Venous Sugars, Mg. per 100 Cc. | | | | | Ileal Venous Sugars, Mg. per 100 Cc. | |
|---|---|---|---|---|---|---|---|
| Dog No. | Start | ½ Hour | 1 Hour | 1½ Hours | 2 Hours | Start | 2 Hours |
| 815 | 83 | 85 | 86 | 88 | 90 | 85 | 97 |
| 1067 | 120 | 139 | 139 | 142 | 142 | | |
| 1068 | 91 | 130 | 132 | 118 | 114 | 101 | 131 |

between the removal of water and absorption of dextrose, but dextrose apparently was absorbed more rapidly than water. The mean loss of fluid was 17.6 per cent, and the mean loss of dextrose, 27.3 per cent.

The peripheral venous sugars showed a tendency to rise. There is no correlation between the percentage of absorption of dextrose and the change in either the peripheral venous or the ileal blood sugars. In fact, of the two experiments in which ileal venous sugars were determined, the larger amount of dextrose absorption was associated with the smaller change in the ileal venous sugar.

38. Hagedorn, H. C., and Jensen, B. N.: Biochem. Ztschr. **135**:46, 1923; **137**:92, 1923.

*The Absorption of a 5 Per Cent Dextrose Solution from the Colon.*—Eight experiments are tabulated in tables 2 and 2*a*. There is a striking difference in the mean loss of fluid in these experiments as compared to the ileal experiments. In only one of the eight experiments did the percentage of absorption of water exceed the minimum percentage of absorption in the first group.

Although the actual amount of dextrose introduced was greater in nearly every experiment, the mean percentage of absorption of dextrose

TABLE 2.—*Five Per Cent Dextrose Solution in Colon of Normal Dog*

| Dog No. | Weight, Kg. | Solution Introduced, Cc. | Percentage Concentration In | Solution Out, Cc. | Percentage Concentration Out | Fluid Volume Change, Cc. | Percentage | Dextrose Introduced, Gm. | Dextrose Out, Gm. | Dextrose Recovered in Washing, Gm. | Total Dextrose Out, Gm. | Dextrose Lost, Gm. | Percentage Dextrose Recovered | Percentage Dextrose Lost |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 383 | 32.0 | 230 | 4.9 | 214 | 4.4 | —16 | — 6.9 | 11.27 | 9.42 | 0.60 | 10.02 | 1.25 | 88.9 | 11.1 |
| 652 | 17.3 | 230 | 4.5 | 220 | 4.0 | —10 | — 4.3 | 10.35 | 8.80 | 0.57 | 9.37 | 0.98 | 90.6 | 9.4 |
| 761 | 16.2 | 200 | 5.0 | 168 | 4.9 | —32 | —16.0 | 10.00 | 8.23 | 0.80 | 9.03 | 0.97 | 90.3 | 9.7 |
| 655 | 12.6 | 204 | 5.0 | 199 | 4.5 | — 5 | — 2.4 | 10.20 | 8.96 | 0.32 | 9.28 | 0.92 | 91.0 | 9.0 |
| 710 | 19.1 | 238 | 5.0 | 224 | 4.8 | —14 | — 5.9 | 11.90 | 10.75 | 0.27 | 11.02 | 0.88 | 92.6 | 7.4 |
| 834 | 10.6 | 190 | 4.7 | 184 | 4.5 | — 6 | — 3.1 | 8.93 | 8.28 | 0.21 | 8.49 | 0.44 | 95.1 | 4.9 |
| 942 | 15.9 | 155 | 5.0 | 141 | 5.0 | —14 | — 9.0 | 7.75 | 7.05 | 0.36 | 7.41 | 0.34 | 95.5 | 4.5 |
| 893 | 9.7 | 154 | 5.0 | 148 | 4.9 | — 6 | — 3.8 | 7.70 | 7.25 | 0.32 | 7.57 | 0.13 | 98.4 | 1.6 |
| Mean..... | | 200 | | 187 | | —13 | — 6.4 | 9.76 | | | 9.02 | 0.74 | 92.8 | 7.2 |

TABLE 2*a*.—*Peripheral and Colic Venous Sugars Following Introduction of 5 Per Cent Dextrose Solution in Colon of Normal Dog*

| | Peripheral Venous Sugars, Mg. per 100 Cc. | | | | | Colic Venous Sugars, Mg. per 100 Cc. | |
|---|---|---|---|---|---|---|---|
| Dog No. | Start | ½ Hour | 1 Hour | 1½ Hours | 2 Hours | Start | 2 Hours |
| 383 | 96 | ... | 93 | ... | 108 | 95 | 78 |
| 652 | 70 | ... | 70 | ... | ... | 83 | 76 |
| 761 | 140 | ... | 140 | ... | 136 | 135 | 138 |
| 655 | 150 | ... | ... | ... | 124 | 142 | 112 |
| 710 | 106 | 106 | 100 | 88 | 85 | 101 | 100 |
| 834 | 105 | 108 | 108 | 99 | 108 | 105 | 107 |
| 942 | ... | 127 | 108 | 121 | 124 | 148 | 121 |
| 893 | 109 | 130 | 126 | 121 | 120 | 113 | 118 |

from the colon was decidedly less. There are, however, a slightly greater mean loss of dextrose than of water and a tendency for the concentration of the solution to fall slightly. Considered from the standpoint of actual loss of dextrose over a two hour period, however, the amount is indeed small, 90 per cent or more having been recovered after a two hour period.

In four animals the peripheral venous sugar changed very little. The changes that did occur were not always in the same direction. In

three experiments the initial blood sugar was high, a condition that is believed to be due to the excitation associated with the induction of anesthesia. The colic venous sugar was likewise high in these animals. There is no indication from the estimations of the colic venous sugar that dextrose was being absorbed rapidly.

Taken as a whole, the data do not support the hypothesis that any considerable amount of dextrose is absorbed in this type of experiment.

Histologic studies of the colon at the conclusion of the experiment showed a normal bowel.

TABLE 3.—*Seven Per Cent Dextrose Solution in Colon of Normal Dog*

| Dog No. | Weight, Kg. | Solution Introduced, Cc. | Percentage Concentration In | Solution Out, Cc. | Percentage Concentration Out | Fluid Volume Change, Cc. | Percentage | Dextrose Introduced, Gm. | Dextrose Out, Gm. | Dextrose Recovered in Washing, Gm. | Total Dextrose Out, Gm. | Dextrose Lost, Gm. | Percentage Dextrose Recovered | Percentage Dextrose Lost |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 586 | 12.2 | 200 | 6.9 | 252 | 5.2 | +52 | +26.0 | 13.80 | 13.23 | 0.42 | 13.65 | 0.15 | 98.9 | 1.1 |
| 601 | 12.0 | 200 | 6.9 | 240 | 4.9 | +40 | +20.0 | 13.80 | 11.76 | 0.22 | 11.98 | 1.82 | 86.9 | 13.1 |
| Mean..... | | 200 | | 246 | | +46 | +23.0 | 13.80 | | | 12.81 | 0.98 | 92.9 | 7.1 |

TABLE 3a.—*Peripheral and Colic Venous Sugars Following Introduction of 7 Per Cent Dextrose Solution in Colon of Normal Dog*

| | Peripheral Venous Sugars, Mg. per 100 Cc. | | | | | Colic Venous Sugars, Mg. per 100 Cc. | |
|---|---|---|---|---|---|---|---|
| Dog No. | Start | ½ Hour | 1 Hour | 1½ Hours | 2 Hours | Start | 2 Hours |
| 586 | 98 | 104 | 104 | 109 | 106 | 107 | 110 |
| 601 | 87 | 95 | 100 | 102 | 94 | 87 | 96 |

*The Absorption of a 7 Per Cent Dextrose Solution from the Colon.*—It was considered advisable to repeat the experiments on the colon, with hypertonic solutions of dextrose. In tables 3 and 3*a* are reported two experiments in which an approximately 7 per cent solution was used. At the end of the two hour period the amount of fluid in the large bowel was greater than that introduced. No definite conclusions can be drawn from the two experiments, but the range of dextrose absorption is within the limits of that obtained when a 5 per cent solution was used.

The peripheral and colic venous sugars tended to rise slightly, but there is a complete lack of correlation between the actual amount of dextrose lost and the changes in the peripheral blood sugar levels.

The histologic studies of the colon removed at the conclusion of the experiment showed only a slight increase in vascularity as evidenced by the greater number of filled capillaries.

*The Absorption of a 10 Per Cent Dextrose Solution from the Colon.*—In tables 4 and 4*a* are tabulated the results obtained from two experiments in which a more concentrated solution was used. As would be expected, the increase in the fluid content of the loop was even greater than when a 7 per cent solution was used. The concentration of dextrose was reduced, but this was largely due to the diluting effect

TABLE 4.—*Ten Per Cent Dextrose Solution in Colon of Normal Dog*

| Dog No. | Weight, Kg. | Solution Introduced, Cc. | Percentage Concentration In | Solution Out, Cc. | Percentage Concentration Out | Fluid Volume Change, Cc. | Percentage | Dextrose Introduced, Gm. | Dextrose Out, Gm. | Dextrose Recovered in Washing, Gm. | Total Dextrose Out, Gm. | Dextrose Lost, Gm. | Percentage Dextrose Recovered | Percentage Dextrose Lost |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 20 | 11.8 | 158 | 9.7 | 214 | 6.0 | +56 | +35.4 | 15.33 | 12.84 | 0.55 | 13.39 | 1.94 | 87.4 | 12.6 |
| 410 | 17.0 | 250 | 9.7 | 339 | 6.2 | +89 | +35.6 | 24.25 | 21.02 | 0.55 | 21.57 | 2.68 | 89.0 | 11.0 |
| Mean..... | | 204 | | 276 | | +72 | +35.5 | 19.79 | | | 17.48 | 2.31 | 88.2 | 11.8 |

TABLE 4*a*.—*Peripheral and Colic Venous Sugars Following Introduction of 10 Per Cent Dextrose Solution in Colon of Normal Dog*

| | Peripheral Venous Sugars, Mg. per 100 Cc. | | | | | Colic Venous Sugars, Mg. per 100 Cc. | |
|---|---|---|---|---|---|---|---|
| Dog No. | Start | ½ Hour | 1 Hour | 1½ Hours | 2 Hours | Start | 2 Hours |
| 20 | 95 | 80 | 95 | 87 | 88 | 94 | 107 |
| 410 | 90 | 95 | 88 | 85 | 82 | 88 | 101 |

of the inflowing fluid. The mean amount of dextrose lost is slightly greater than that lost when a 5 per cent solution was used.

The peripheral venous sugar was lower at the conclusion of the experiment than at the beginning, while the colic venous sugar had increased in each experiment by 13 mg. per hundred cubic centimeters of blood.

The sections of the bowel removed at the conclusion of the experiment were similar to those removed from the previous group in that the only evidence of change was an increase in the number of filled capillaries.

*The Absorption of a 5 Per Cent Dextrose Solution from the Colon of the Pancreatectomized Dog.*—Five experiments are reported in tables 5 and 5*a*. The hyperglycemia in these animals was considerably greater

than that of the animals in group 2, who were excited during the induction of the anesthesia. The mean percentage of fluid absorbed was slightly greater than when a similar concentration of dextrose was placed in the colon of the normal dog. However, if the data from dog 387 are eliminated, the percentage of fluid absorbed is within the range of the normal animals. There is no evidence that dextrose is more rapidly absorbed under the conditions of this experiment. The percentage range of dextrose absorption in the five experiments is large,

TABLE 5.—*Five Per Cent Dextrose Solution in Colon of Pancreatectomized Dog*

| Dog No. | Weight, Kg. | Solution Introduced, Cc. | Percentage Concentration In | Solution Out, Cc. | Percentage Concentration Out | Fluid Volume Change, Cc. | Percentage | Dextrose Introduced, Gm. | Dextrose Out, Gm. | Dextrose Recovered in Washing, Gm. | Total Dextrose Out, Gm. | Dextrose Lost, Gm. | Percentage Dextrose Recovered | Percentage Dextrose Lost |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 387 | 9.8 | 144 | 3.75 | 110 | 3.3 | —34 | —23.6 | 5.40 | 3.63 | 0.83 | 4.46 | 0.94 | 82.6 | 17.4 |
| 390 | 9.9 | 232 | 4.7 | 220 | 4.7 | —12 | — 5.1 | 10.90 | 10.34 | 0.56 | 10.90 | 0.00 | 100.0 | 0.0 |
| 362 | 9.9 | 171 | 4.95 | 162 | 4.7 | — 9 | — 5.2 | 8.46 | 7.61 | 0.58 | 8.19 | 0.27 | 96.8 | 3.2 |
| 450 | 9.9 | 207 | 4.5 | 198 | 3.7 | — 9 | — 4.3 | 9.31 | 7.33 | 0.33 | 7.66 | 1.65 | 82.3 | 17.7 |
| 540 | 10.9 | 233 | 4.8 | 220 | 4.3 | —13 | — 5.5 | 11.18 | 9.46 | 0.72 | 10.18 | 1.00 | 91.1 | 8.9 |
| Mean..... | | 197 | | 182 | | —15 | — 9.3 | 9.05 | | | 8.28 | 0.77 | 90.6 | 9.4 |

TABLE 5a.—*Peripheral and Colic Venous Sugars Following Introduction of 5 Per Cent Dextrose Solution in Colon of Pancreatectomized Dog*

| | Peripheral Venous Sugars, Mg. per 100 Cc. | | | | | Colic Venous Sugars, Mg. per 100 Cc. | |
|---|---|---|---|---|---|---|---|
| Dog No. | Start | ½ Hour | 1 Hour | 1½ Hours | 2 Hours | Start | 2 Hours |
| 387 | 278 | 261 | 276 | 265 | 260 | 250 | 290 |
| 390 | 315 | 299 | 311 | 299 | ... | 303 | 268 |
| 362 | 225 | 196 | 175 | 220 | ... | 244 | 261 |
| 450 | 325 | 310 | 315 | 298 | 284 | 263 | 295 |
| 540 | 258 | 253 | 271 | 279 | 271 | 252 | 261 |

but the mean dextrose absorption is approximately the same as in the previous experiments. Again there is a tendency toward a reduction in the concentration of the dextrose in the colon.

The peripheral and colic venous sugars show no consistent changes. There is a tendency for the peripheral venous sugar to decrease, but in dog 540 it increased. The colic venous sugars rose in four of the five experiments, and there appears to be some correlation between the percentage of absorption of dextrose and the rise in the colic venous sugar. In the one experiment in which a fall occurred in the colic venous sugar, there was no evidence of dextrose absorption.

The sections of the colon were entirely normal.

*The Absorption of a 5 Per Cent Solution of Dextrose from the Colon of the Hypoglycemic Dog.*—The results in two animals made hypoglycemic by the subcutaneous injection of 10 units of insulin per kilogram of body weight one-half hour before beginning the experiment are reported in tables 6 and 6*a*. The percentage of fluid absorbed is small indeed, the lowest for any group in which approximately isotonic solutions were used. The striking feature, however, is the

TABLE 6.—*Five Per Cent Dextrose Solution in Colon of Insulinized (Hypoglycemic) Dog*

| Dog No. | Weight, Kg. | Solution Introduced, Cc. | Percentage Concentration In | Solution Out, Cc. | Percentage Concentration Out | Fluid Volume Change, Cc. | Percentage | Dextrose Introduced, Gm. | Dextrose Out, Gm. | Dextrose Recovered, in Washing, Gm. | Total Dextrose Out, Gm. | Dextrose Lost, Gm. | Percentage Dextrose Recovered | Percentage Dextrose Lost |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 161 | 16.6 | 240 | 5.2 | 228 | 4.2 | —12 | — 5.0 | 12.50 | 9.57 | 0.26 | 9.83 | 2.67 | 78.7 | 21.3 |
| 759 | 17.2 | 240 | 4.95 | 238 | 3.8 | — 2 | — 0.8 | 11.88 | 8.97 | 0.29 | 9.26 | 2.62 | 77.9 | 22.1 |
| Mean..... | | 240 | | 233 | | — 7 | — 2.9 | 12.19 | | | 9.54 | 2.64 | 78.3 | 21.7 |

TABLE 6*a*.—*Peripheral and Colic Venous Sugars Following Introduction of 5 Per Cent Dextrose Solution in Colon of Insulinized (Hypoglycemic) Dog*

| Dog No. | Before Insulin | Peripheral Venous Sugars, Mg. per 100 Cc. | | | | | Colic Venous Sugars, Mg. per 100 Cc. | |
|---|---|---|---|---|---|---|---|---|
| | | Start | ½ Hour | 1 Hour | 1½ Hours | 2 Hours | Start | 2 Hours |
| 161 | 84 | 81 | 72 | 55 | 41 | 29 | 74 | 37 |
| 759 | 135 | 99 | 78 | 67 | 55 | 57 | 85 | |

relatively rapid absorption of dextrose, a mean of 21.7 per cent of that injected being lost in the two hour period. In these experiments dextrose was leaving the colon much more rapidly than was water.

The peripheral and colic venous sugars fell throughout each experiment so that, even though considerable dextrose was absorbed, the insulin was sufficient to prevent it from maintaining a constant sugar level. It must be considered, however, that the dose of insulin was unusually large. This dosage was used purposely in order to determine whether the rate of absorption from the colon could be increased under the conditions of a marked blood dextrose deficit.

*The Effect of the Introduction of an Inert Substance (Paraffin Oil) into the Colon on Blood Sugar Levels.*—Two experiments were per-

formed (table 7) in each of which paraffin oil similar in volume to the dextrose used in the earlier experiments was placed in the isolated colon. Specimens of blood were removed from the peripheral and colic veins. These showed slight variations. The colic venous sugars tended to go to lower levels at the end of the two hour period.

*Bacterial Action.*—The effect of bacterial action and handling on a known amount of dextrose solution in a completely excised colon, from a freshly killed animal, washed and prepared in a manner similar to the method used in the intact animal, was also tested. The 75 cc. of a 4.7 per cent solution of dextrose which was introduced contained 3.31 Gm. of dextrose. The bowel and its contents were placed in a beaker and incubated at 37.5 C. for two hours. At the end of that period, 70 cc. of the solution was recovered which contained 3.08 Gm. of dextrose. The washings contained an additional 0.14 Gm. of dextrose, bringing

TABLE 7.—*Peripheral and Colic Venous Sugars Following Introduction of Paraffin Oil in Colon of Normal Dog*

| Dog No. | Weight, Kg. | Oil, Cc. | Peripheral Venous Sugars, Mg. per 100 Cc. | | | | | Colic Venous Sugars, Mg. per 100 Cc. | |
|---|---|---|---|---|---|---|---|---|---|
| | | | Start | ½ Hour | 1 Hour | 1½ Hours | 2 Hours | Start | End |
| 1034 | 8.8 | 132 | 102 | 103 | 103 | 96 | 104 | 102 | 92 |
| 1046 | 7.7 | 154 | 113 | 115 | 114 | 122 | 112 | 106 | 101 |

the total amount recovered to 3.22 Gm. The dextrose lost through possible bacterial action and failure to recover was estimated at 2.6 per cent of the quantity introduced.

*Determination of Nondextrose Copper-Reducing Substances in the Solutions Exposed to the Mucous Membrane of the Bowel.*—Of the 210 cc. of tap water introduced into the colon of the living dog, but 150 cc. of fluid was recovered after the lapse of two hours. Titration was done by the Benedict method.[37] It was impossible to arrive at an end-point by using the entire 150 cc. recovered from the loop. Calculated at this point, the concentration of the reducing substances would be less than 0.03 per cent, and, from the color of the copper solution remaining, it would be safe to state that the amount was even lower than this. Even at the former level, the quantity is insignificant.

This experiment likewise demonstrates that tap water is readily and quickly taken up by the colon to the extent of 28.5 per cent in this one case.

Venous blood sugar determinations were made as well in this dog. The determinations of the peripheral and colic venous blood sugar showed little change.

COMMENT

It is evident from these experiments that there is a marked difference in the ability of the ileum and colon of the dog to absorb dextrose. In a two hour period, the normal anesthetized dog being used, the rate of absorption of dextrose from solutions varying from approximately 5 to 10 per cent was indeed small. The percentage of dextrose absorption is slightly greater than that given by McNealy and Willems [2] for 5 per cent solutions, but this may be due to the use of the large rectal ampulla. There appears to be a slightly greater absorption when 10 per cent solutions are used, but even here the actual amount absorbed was so small that even though the same rate could be maintained for a twenty-four hour period, the total dextrose absorbed would amount to only 27.7 Gm.

In two of the pancreatectomized animals the percentage absorption was considerable, but when calculated for the total amount absorbed, it is of little significance, a mean in all the pancreatectomized dogs of only 0.77 Gm. being absorbed over the two hour period.

It is interesting to note that, when a definite blood sugar deficit was maintained, as in the experiments on the hypoglycemic dogs, the percentage of absorption of dextrose was higher than in any of the colonic experiments and approximated the rate of absorption from the ileum. It would appear from these experiments that there may be some foundation in the observation of clinicians that diabetic persons in shock are improved by rectally administered dextrose. However, when time is an essential factor, it would not be wise to place the sole reliance on this method of administration of dextrose because the absorption is so slow.

The findings of McNealy and Willems [2] in regard to the rate of water removal when solutions of dextrose are placed in the large bowel have been confirmed. Tap water is absorbed much more rapidly. With the exception of one animal (dog 387, table 5), nothing approximating this rate of removal was observed in any of the experiments on the colon in which dextrose was used. Clinical experience has demonstrated that this is also true in man.

The blood sugar studies indicate that they are of little use as an indication of absorption where the rate of absorption is small. The findings in normal subjects presented in this paper are in essential agreement with those of Scott and Zweighaft.[3] There appears to be no direct correlation between the amount of dextrose absorbed and the peripheral blood sugar level. This may be due to the slow rate of absorption and to the stimulation of some mechanism which increases dextrose withdrawal from the blood stream. In the experiments in

which 7 and 10 per cent solutions of dextrose were placed in the colon, and in the pancreatectomized dogs, the colic venous sugars show some correlation with the amount of dextrose removed from the colon during the two hour period.

## SUMMARY

Dextrose solutions are absorbed at a low rate when placed in the entire colon of the dog. Hypertonic solutions (10 per cent) are absorbed little faster than are isotonic solutions. When a marked dextrose deficit occurs in the blood, dextrose can be absorbed from the colon approximately as rapidly as it can be from a low ileal loop of the noninsulinized dog. The presence of dextrose in the solution in the colon, in the concentration used, causes a retardation in the rate of water absorption. The total amount of dextrose which can be administered and absorbed from the colon under the best conditions would appear to be too small for any considerable immediate therapeutic effect.

# SELECTIVE STAINING OF DISEASED AREAS IN CARTILAGE BY INTRA-ARTICULAR INJECTION OF DYES

## AN EXPERIMENTAL CADAVER STUDY, WITH SPECIAL REFERENCE TO ARTHROSCOPY

MICHAEL S. BURMAN, M.D.
NEW YORK

The intra-articular injection of dyes is not a new procedure, though practiced only from the experimental standpoint to determine the absorptive capacity of the synovial membrane and the paths of absorption. A review of the literature indicates that no attention has been paid to the gross staining of cartilage by dyes. Tillmanns, in 1876, injected berlin blue into the bony canals of the amputated femurs of his experimental animals, after cutting away the bony plate that intervenes between the femur and the joint cavity. He intended to study the absorptive power of the synovia, without injuring either synovia or capsule. In seven cases, he noted a superficial staining of cartilage, easily washed out by a stream of water. Schreiber of Tübingen, in 1904, in analyzing the constituents of Belchier's madder, noted that purpurin, injected into the dorsal lymph sac of the frog, stained cartilage vitally a purple hue.

The gross staining reactions of cartilage in disease, as in jaundice and hematoporphyrinemia, are interesting. One deals here with pigments circulating in blood. Whether this is the case in ochronosis, which stains cartilage blackish, is still mooted. It is affirmed in all textbooks of pathology that in jaundice cartilage is not stained *intra vitam*. We have had several occasions to verify this. Schmorl has shown that the degenerated cartilage of intervertebral disks does take up the icteric stain *intra vitam*. It is the custom in the Pathologic Institute in Dresden to remove the entire right femur for examination. On the right side, then, in all cases of jaundice, the cartilage of the patella, of the femoral and tibial condyles and even of the menisci was stained green, the intensity of color varying with the length of exposure to air. When the left

All the work on cadavers was done at the Pathological Institute of the Krankenhaus der Friedrichstadt-Dresden, through the kindness of Geheimrat Schmorl, during a period of time when I was Scholar of the Henry W. Frauenthal Traveling Scholarship. The animal work was done at the Hospital for Joint Diseases, New York, with the assistance of Dr. M. Langsam and through the kindness of Dr. Henry Jaffe.

or untouched knee joint was opened or was examined through the arthroscope, the cartilage and menisci were noted as definitely not stained.

This work was undertaken as a collateral study to arthroscopy,[1] following a suggestion of Professor Schmorl that it would be interesting to observe through the arthroscope the formation of arthritis experimentally produced by the use of colored irritants. I determined to test the general effect of a dye on the cartilage of cadavers recently deceased. I used the standard laboratory solutions of the various dyes used for tissue staining, diluted about 1 : 10 with water. The dye used was injected into the joint, usually the knee joint, and was immediately washed out by continuous irrigation. In many cases, the joint was then examined through the arthroscope to determine just what had happened in the interior of the joint. After a thorough examination, the findings were verified by opening the joint.

## RESULTS

The following is a report of the work done.

*Eosin.*—Eosin apparently stains eroded areas on cartilage selectively and instantaneously; that is, normal or almost normal cartilage does not stain. The usual eroded areas on the under surface of the patella and on top of the intercondyloid notch stain particularly well. The stain is deep in the eroded areas but does not extend to bone. The greater the erosion, the deeper is the stain. Degenerated areas in cartilage, showing no particular erosion, stain from a light to a deep pink, though with not as great a selectivity as areas of erosion. Areas of "Wucherung" or overgrowth of new cartilage or fibrous tissue may stain better and deeper than small areas of erosion. Eosin, injected into a normal joint, will not stain cartilage. When the joint is opened and eosin is poured over the cartilage of the opened joint, all cartilage, whether normal, degenerated or eroded, stains almost uniformly. This may be due to exposure to air—the only explanation we can offer thus far for this phenomenon of paradoxical staining. Acid, such as hydrochloric acid, injected into the joint previous to the injection of the dye does not alter the staining powers of the dye.

Most of the joints into which eosin was injected were those of elderly people having arthritis of varying degree. Not only does cartilage stain, but it is seen that the synovial membrane, the crucial ligaments and the semilunar cartilages (menisci) also stain. The semilunar cartilages stain variously, best on their superior and inferior surfaces, but never in their depths. The staining is more pronounced if the

1. Burman, M. S.: Arthroscopy or the Direct Visualization of Joints. An Experimental Cadaver Study, J. Bone & Joint Surg. **13**:669 (Oct.) 1931.

cartilage is degenerated, and if the inner free edge is irregular and fuzzy. The synovial membrane does not stain uniformly or deeply, but in scattered areas, sometimes more or less diffusely, not depending apparently on sites of degeneration. The infrapatellar fat pad has been noted to be stained through and through, indicating that there is a rapid diffusion of the dye through the synovia. Free synovial villi stain a delicate pink at times. The crucial ligaments, especially the anterior crucial ligament, stain only slightly. The color does not deepen on standing, when the opened joint is exposed to air.

The stain is always superficial and is present only in the upper cell layers of cartilage. Light scraping of the cartilage with a knife removes the stained areas easily and indicates the superficialness of the stain.

If hematoxylin is injected into the joint first and then eosin, after the hematoxylin has been washed out it is noted that the colors may mix or be separate, or that the pink of the eosin may overlie a clearly underlying blue of the hematoxylin. If, in the opened joint, hematoxylin is poured over a previously eosin-stained joint, one can see the blue of the hematoxylin overlying the pink of the eosin, with no tendency to fusion of colors. Each stain is separate. If in the opened knee joint, one half of the tibial condyles are stained with alcoholic eosin and one half with watery eosin, one notes that the resultant stains are uniform and identical.

Occasionally, when the dye is injected as from an inner puncture, the dye is noted to be confined to the inner half of the joint. This may be due to the fact that the joint is divided in halves by fat or adhesions that prevent the further spread of the dye.

Alcoholic eosin was injected into a knee joint in each of two adult rabbits. There was no staining of the cartilage, which was normal, though somewhat brownish, but a deep pink staining of the synovia and soft tissues took place. In one case, the menisci stained slightly. When the dye was poured over the opened joint, the cartilage stained relatively uniformly but not deeply. The menisci stained well.

Alcoholic and watery eosin stain cartilage alike.

Through the arthroscope, it is noted that the joint space is colored a fluorescent green, while the cartilage and soft tissues stain pink. Eroded areas are well seen. There is no metachromasia.

Eosin was injected into ten joints, alcoholic eosin into five and watery eosin into five. Eosin may be said to possess powers of selective staining, with particular predilection for eroded areas in cartilage and less for degenerated areas.

*Hematoxylin.*—Hematoxylin was injected into three or four joints. The staining of cartilage is slight, instantaneous and superficial, and not washable, uniform, metachromatic or selective, though degenerated areas

seemed to take the stain well. Staining is never widespread. In one case, the hematoxylin was injected into the knee joint of a deeply jaundiced man (carcinoma of the pancreas). The stain was slight, and, on exposure of the cartilage to air, after the joint was opened, the blue of the hematoxylin mixed itself with the yellow-green of the jaundiced cartilage, producing a weird color effect.

If hematoxylin is poured over the opened joint, it does not stain the cartilage uniformly, but a bit more diffusely than in the closed joint. The combination of eosin and hematoxylin has been already noted.

The semilunar cartilages stain on their superior and inferior surfaces, though not diffusely. The free edge may stain a bit more deeply. The synovial membrane and the crucial ligaments stain only slightly.

Acid hematoxylin (a brown solution) stains cartilage neither in the closed joint nor in the open joint.

Hematoxylin, as indicated in these few experiments, seems to be a weak dye, with no particular power of selectivity.

*Methylene Blue.*—Methylene blue was injected into five joints, the alcoholic solution into three and the watery one into two. Two of the joints showed absolutely normal cartilage. Staining of cartilage, with either the alcoholic or the watery solutions, is instantaneous, very diffuse, superficial, nonselective and not washed away by a strong stream of water, both in normal and in arthritic joints. Cartilage stains diffusely and deeply blue, without regard to the nature of the cartilage, though certain areas in cartilage do not stain at times. The synovial membrane and its villi are well stained. The menisci stain completely both on their two surfaces and on their free edge. The crucial ligaments stain particularly well. The quadriceps bursa stains a deep blue.

Metachromasia of soft tissues and of cartilage is definitely noted here, the color gamut being from blue to blue purple to red purple. This altered staining disappears on exposure to air.

In one case, only the inner half of the joint (an inner puncture being used) was stained, fat apparently blocking the spread of the dye to the outer half of the joint.

Pouring the dye over the opened joint does not increase the intensity of stain or alter its type or extent.

Alcoholic methylene blue was injected into a knee joint of each of two rabbits, with results identical to the foregoing ones.

Through the arthroscope, after the dye has been washed out, the stained areas are clearly visible. The joint space is a peculiar blue brown.

*Sudan III.*—This dye was used in two cases. Once, it was injected into the normal shoulder joint of a young man, with no staining of cartilage or synovia. In the second case, it was poured over the opened

knee joint of a man 34 years old, dead of tuberculosis; no immediate staining resulted. After a few minutes' exposure, fat was noted to be stained an orange yellow, and the fibrillar cartilage of the patella a slight yellow.

*Alcoholic Methyl Violet.*—This dye gave a strong, diffuse, blue-violet staining of all structures within the knee joint in the two cases in which it was used. Cartilage stains blue-violet, with possibly a slight predilection for degenerated areas. Synovia and its villi stain deeply blue. The semilunar cartilages stain diffusely well. The crucial ligaments stain well also. Metachromasia was noted in one case.

The stain deepens on exposure to air. If the dye is poured over the opened joint, the type or the extent of the staining is not changed. The staining of cartilage is superficial and instantaneous.

*Lithium Carmine.*—This dye, when injected into the knee joint (one case), stains instantaneously, very superficially and with an apparent predilection for diseased areas in cartilage, i.e., selectivity in staining. When it is poured over the opened knee joint, it does not stain cartilage further.

*Neutral Red.*—This dye was used in three knee joints. The stain is dark red, instantaneous, superficial and not washable; it is definitely selective for eroded areas in cartilage, and possibly less so for degenerative, fibrillar areas. Where the cartilage is fibrillar, the stain may then be diffuse. In one case, in an area of apparently normal cartilage, a deep staining took place; on cutting into the cartilage, a brown, degenerated area was observed beneath the surface. Possibly, then, this dye has the power to reveal early areas of degeneration in cartilage, not as yet visible to the eye. The menisci of the knee joint, the crucial ligaments and the synovia with its villi also stain a little.

When the dye is poured over the opened joint, one also notes that this dye has a definite predilection and selectivity for eroded and diseased areas in cartilage, though the staining here is a bit more diffuse.

A section of stained cartilage was examined by frozen section. It was noted that the stain was very superficial and confined to the upper cell layers, and stained the capsule, cells and intercellular substance equally well. The space between the capsule and cell, however, did not stain.

*Bismarck Brown.*—This dye was used in one case, giving a slight brown tinge to the cartilage. Poured over the cartilage of the opened joint, it did not stain.

*Two Per Cent Gentian Violet.*—This dye (used in one knee joint) stains irregularly, diffusely, instantaneously, superficially and without powers of selectivity. The staining is deep violet blue. All structures

stain almost equally well (cartilage, crucial ligaments, menisci, synovia). When the dye is poured over the opened joint, similar staining results. The staining capacities of the dye were examined through the arthroscope.

*Concentrated Orange Solution.*—The dye was injected into one hip joint with no resultant staining. The dye poured over the opened joint stained cartilage and synovial membrane slightly yellowish orange.

*Toluidine Blue.*—The dye was injected into one knee joint. Certain areas in cartilage, possibly degenerated, stained blue and also metachromatically. The stain is instantaneous, superficial, not washable and possibly selectively weak in staining. Menisci, crucial ligaments and the inner surface of the synovia stained a little. The metachromasia (blue to red purple) faded on opening the joint. The dye poured over the opened joint causes a slightly increased bluish staining of cartilage.

*Concentrated Alcoholic Solution of Thionine.*—When this dye is spilled over an opened joint, it stains cartilage and synovia very slightly, the stain deepening on standing.

*Alum Carmine.*—When this dye is injected into the closed knee joint, it does not stain; when it is poured over the opened joint, it stains cartilage and synovia slightly, superficially and unevenly.

*Litmus Solution.*—To test the action of indicators in their ability to stain joint cartilage, a watery solution of blue litmus (alkaline) was injected into the knee joint of one patient. It is to be noted that the water of Dresden is alkaline. No accurate chemical test of alkalinity was made. The color of the solution did not change, which indicates that the $p_H$ of the joint fluid after death was still roughly alkaline. There was a slight bluish, superficial, easily washable staining of the joint cartilage. When litmus was poured over the opened joint, there was only a slight staining of cartilage, easily washed away by a stream of water. The color of the litmus did not change.

*Bile.*—A weak solution of bile was injected into the knee joint in one case with no resultant staining. No staining occurred when the bile was poured over the opened knee joint. The solution was evidently too weak to stain. It was noted that a drop of concentrated bile, poured accidentally from an opened gallbladder over the patella, stained it a green yellow, the stain being deep in color and not washed away by a stream of water.

## COMMENT

It can then safely be concluded that there are dyes that stain cartilage slightly or not at all, dyes that are diffuse in action, and dyes that are selective. The term "selectivity of action" means that these

dyes stain only eroded or degenerated areas in cartilage and leave normal cartilage unstained.

The course then is clear—to find those dyes that are selective and harmless. A series of experiments should be undertaken to determine the nature of dyes that stain selectively, the amount of dye necessary for use in a joint, the reaction of the joint to the dye, the absorption of the dye, the ability or inability of the dye to cause an experimental or clinical arthritis, the physical, chemical and biologic reasons that underlie selectivity, with special reference to the chemical nature of the dye and the biologic properties of the diseased area. Once this is determined by patient research, it will be possible to utilize these new facts in arthroscopy. Stained areas are clearly outlined through the arthroscope, much better than unstained areas, especially areas of erosion, which are difficult to visualize.

It is possible that the staining reactions described may not occur in living cartilage in the living person. The few animal experiments performed by me indicate this premise to be wrong. Whether one can call the intra-articular injection of dyes for the purpose of staining cartilage vital staining is questionable; it surely cannot be so called in the usually accepted sense of the term. What relation changes in the alkalinity of the synovial fluid bear to the staining of cartilage is not as yet known. Even after death, it appears that the synovial fluid, remains alkaline, and rarely in life does it reach a $p_H$ lower than 7. It may be probable that the sometimes oily fluid exerts a protective effect against cartilage staining. Why there should be a difference between the staining powers of cartilage in the opened and in the closed joint is still conjectural. It is important to find a blue dye that stains selectively, since a red dye gives poor color contrast, especially in hyperemic or other inflammatory conditions of the joints.

## CONCLUSION

Of the several dyes examined, eosin, neutral red and lithium carmine seem to stain diseased areas in cartilage selectively. This selective staining is of definite value in arthroscopy, delimiting, as it does, areas of disease in color, thus rendering visualization easy. The work presented here is only the most preliminary of studies.

# FORTY-NINTH REPORT OF PROGRESS IN ORTHOPEDIC SURGERY

JOHN G. KUHNS, M.D.

EDWIN F. CAVE, M.D.

SUMNER M. ROBERTS, M.D.
AND
JOSEPH S. BARR, M.D.
BOSTON

JOSEPH A. FREIBERG, M.D.
CINCINNATI

JOSEPH E. MILGRAM, M.D.
NEW YORK

GEORGE PERKINS
LONDON, ENGLAND
AND
PHILIP D. WILSON, M.D.
Advisory Editor
BOSTON

This Report of Progress is based on a review of 195 articles selected from 359 articles dealing with orthopedic surgery appearing in the medical literature approximately between April 5 and July 30, 1932. A few selected articles of an earlier date are included. Only those papers that seemed to represent progress have been chosen for review.

## CONGENITAL DEFORMITIES

*Open Reduction of Congenital Dislocation of the Hip.*—Howorth and Smith [1] reported observations in 72 cases of congenital dislocation of the hip in which the patients were treated by open operation from January, 1920, to July, 1929. In 26 cases the dislocation was bilateral. The average age was 4 years and 8 months. In the treatment of 46 of the 82 hips, previous attempts at closed reduction had failed.

The operations used were as follows: (1) simple reduction, 54 per cent; (2) gouging of the acetabulum followed by reduction, 20 per cent; (3) shelf operation, 11 per cent. In two hips it was necessary to reshape the femoral head. The anatomic and functional end-results were summarized; reduction was maintained in 66 per cent. Eighteen months after the first operations subluxation occurred in 31 per cent. Dislocation recurred in only 8 per cent. A good functional result was gained in 67 per cent.

1. Howorth, M. B., and Smith, H. W.: J. Bone & Joint Surg. **14**:299, 1932.

Kidner [2] reviewed briefly the controversy between the schools advocating open and closed reduction of congenital dislocated hips. He has become convinced that open reduction gives the better result except in the rare young patient in whom the gentlest manipulation results in reduction.

He stated that the great obstacle to reduction, as shown on the operating table, was a redundant adherent capsule and not bony, cartilaginous or muscular changes as many workers had assumed. He found that little force was necessary usually to obtain reduction if the capsule was adequately freed. His operative approach consisted in an anterior incision extending downward from the anterior superior spine, retracting the sartorius medially and the tensor fascia and gluteus medius laterally. The capsule was reflected downward from the ilium as far as the superior border of the acetabulum. The capsule was then incised longitudinally, and the head of the femur was replaced in the acetabulum, which was enlarged if necessary. The redundant capsule was used as a reenforcing ligament. The leg was immobilized in abduction and internal rotation for from eight to twelve weeks. After physical therapy, walking was permitted. Kidner stated that inversion of the neck usually disappeared after reduction and in any case did not affect the end-result. He stated that in twenty-five cases in which operations were performed there was one postoperative death. In the others good results were obtained. There were no recurrences of the dislocation.

[ED. NOTE.—Open operation in congenital dislocation of the hip is coming into greater favor, particularly in the older or more difficult cases, because of the pathologic changes that often prevent reduction by manipulation. The end-results tabulated here, while on a small number of cases, are encouraging.]

### DISTURBANCES IN BONE GROWTH

*Osteitis Deformans.*—Belden and Bernheim [3] made a study of 26 patients with osteitis deformans and as a result concluded that Paget's disease was a metabolic unbalance governed by the ductless glands. They believed that the apparent overaction of the parathyroid glands could best be controlled by a proper dietary and medical regimen. This was as follows: viosterol, 10 drops three times a day; tomato juice, 6 ounces (178 cc.) three times a day, and calcium lactate, 40 grains (2.6 Gm.) twice a day. Improvement was observed in all of the patients under this treatment.

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2. Kidner, F. C.: South. M. J. **25**:350, 1932.

3. Belden, W. W., and Bernheim, A. R.: Radiology **18**:324, 1932.

*Roentgenography of the Bones in Gaucher's Disease.*—Reiss and Kato [4] studied 3 cases of Gaucher's disease in regard to the changes in the bones. The most constant and typical changes were observed in the lower end of the femur, which usually had a moth-eaten, punched-out appearance. There was an osteoporosis throughout the shaft. Pathologic fracture without bony displacement was common. The other long bones were frequently involved. Compression of the vertebrae was observed without a disappearance of the intervertebral disk, although the disks might be invaded extensively by the disease.

*The Growth of Bone.*—Jansen,[5] in the Lady Jones Memorial Lecture delivered at Liverpool on Feb. 17, 1931, traced the development of certain concepts in regard to the formation and growth of bone. He showed how both excessive and subnormal functional pressure led to the absorption of lime salts from bone, and that an enhanced deposition of lime salts occurred somewhere between these two extremes. He believed that in exercise the bones were as well developed as the muscles. Two aspects of the increased vulnerability of the rapidly growing cells of bone were given: (1) Injurious agents of all kinds might cause feebleness of growth. (2) The signs of feebleness of growth were given in three degrees: (*a*) The slight degree was characterized only by muscular weakness, weak feet, a prominent abdomen, round shoulders and blue hands and feet; there was usually an overgrowth in adolescence. (*b*) The moderate degree was represented by the knock-kneed child, neither too tall nor too short. (*c*) The severe degree was characterized by severe muscular weakness; all of the cartilages of growth were affected, and the entire skeleton lagged behind the normal in growth. The severe form of enfeeblement of growth was observed in the first few years of life. Enfeebled bone substance showed two characteristics: increased fatigability and increased irritability. By studying the quantitative changes in growth in the locomotor apparatus, evidence of a feeble constitution might be obtained. The discovery and removal of the causes of such enfeeblement of growth would remove much disease and crippling of the human race.

[Ed. Note.—Jansen's views on the various factors influencing the growth of bone are thought provoking and merit consideration and for this reason they are worth while even if we are unable to agree with all of his conclusions.]

## NEOPLASMS

*Fibrosarcoma of Bone.*—Geschickter [6] stated that the osteogenic portions of the bone do not give rise to sarcoma of the true spindle cell

4. Reiss, O., and Kato, K.: Gaucher's Disease: Clinical Study, with Special Reference to Roentgenography of Bones, Am. J. Dis. Child. **43**:365 (Feb.) 1932.

5. Jansen, M.: Surg., Gynec. & Obst. **54**:175, 1932.

6. Geschickter, C. F.: So-Called Fibrosarcoma of Bone: Bone Involvement by Sarcoma of the Neighboring Soft Parts, Arch. Surg. **24**:231 (Feb.) 1932.

type. Connective tissue tumors in bone arise from fibroblasts with a tendency to bone formation or from precartilaginous connective tissue destined to form bone via the intracartilaginous route. His study of thirty-one cases showed that the histologic composition of the new growth was a more reliable index of its clinical and pathologic behavior than its anatomic location or apparent relationship to bone. Fibrospindle cell tumors should be studied in regard to the transition from oat cell to spindle cell to fibrospindle cell to adult fibroblasts. The more primitive the connective tissue cell, the more malignant was the tumor. In the undifferentiated oat cell type, neither excision nor roentgen therapy offered more than temporary relief. In neurogenic tumors involving bone, a similar microscopic gradation could be made. The more malignant the tumor, the greater was the number of large pleomorphic nuclei and the more closely packed the spindle cells. The prognosis was extremely bad, death usually occurring in two years. The author mentioned that bone was sometimes invaded by connective tissue tumors arising from outside the bone which gave a similar clinical picture, such as angiomas, myosarcomas and lipomas. When the fibrosarcoma was not of the oat cell type, an attempt to eradicate the disease locally was justifiable. In the oat cell type, immediate amputation was indicated. Amputation was the treatment of choice in neurogenic sarcoma involving the bone. For angiomas, local excision followed by irradiation seemed the best treatment. Local excision was advocated for lipomas and amputation for myosarcomas.

## THE BACK

*Backache; Anatomic Consideration.*—Willis [7] reported his studies on the anatomy of many spinal columns at Western Reserve University. He was particularly interested in the anomalous developments, such as spina bifida occulta, asymmetric sacralization and the "separate neural arch," a defect in one or both laminae occurring between the superior and inferior articular processes of the lumbar vertebrae, most often the latter. The relationship of this last anomaly to spondylolisthesis was, as pointed out by the author, well known. Willis found the defect present in 79 instances in a study of 1,520 skeletons, an incidence of 5.9 per cent.

*Spondylolisthesis.*—Meyerding [8] reviewed the findings in 207 cases of spondylolisthesis; 148 were in male patients and 59 in female patients. The condition was found to be due to instability of the lumbosacral articulation and to congenital defects in the lumbosacral region. A number of patients had spondylolisthesis without symptoms. The

7. Willis, T. A.: J. Bone & Joint Surg. **14**:267, 1932.

8. Meyerding, H. W.: Surg., Gynec. & Obst. **54**:371, 1932.

chief symptom was backache, with or without radiating pain. Prominence of the sacrum and a shortened torso were commonly observed. Neurologic disturbances were rare. X-ray pictures, particularly lateral ones, helped greatly in the diagnosis. While spinal support often relieved the symptoms, the author advised fusion of the sacrum to the lower lumbar spine.

*Typhoid Spine.*—Wang and Miltner [9] reported 2 cases of typhoid spine, 1 of which also presented a destructive arthritis of the sacro-iliac joint. There was complete recovery in both cases, with bony ankylosis of the spines in the involved areas. The treatment used was prolonged recumbency followed by a spinal support. There was bacteriologic verification of the diagnosis in both cases.

*Gibbus Resulting from Tetanus.*—Ciaccia [10] collected cases from the literature, and added 2 of his own in which gibbus developed following tetanus. All of the lesions were dorsal in location excepting 2 in the lumbar region. They were characterized by an absence of destruction of the intervertebral disks, an absence of abscess formation and partial collapse of from one to three vertebral bodies. Various etiologic factors were discussed at length; chief among these was the spontaneous vertebral collapse in the presence of maintained muscular spasm. In 1 case Ciaccia fused the spine, and in the other he obtained a satisfactory result by conservative therapy.

### SUPPURATIVE ARTHRITIS

*Suppurative Arthritis of the Hip.*—From a study of 18 septic hips in 17 children, Caldwell [11] concluded that it was important to establish the diagnosis of such a condition early and to determine, if possible, whether the infection was primarily an osteomyelitis of the femoral neck or whether it originated from the synovial lining of the joint. In all of the 17 cases the infection was of hematogenic origin. To wait for roentgen evidence in the presence of sepsis was often disastrous, because this rarely occurred before two weeks had elapsed. He favored early aspiration of the joint as a means of establishing the diagnosis. Twelve hips were drained by anterior incisions, 2 posteriorly and 4 by incisions over the inner side of the thigh, where abscesses were pointing. Postoperative traction in abduction was considered most essential to prevent dislocation. In cases in which there was a primary osteomyelitis or epiphysitis, ankylosis of the joint was apt to result. Frequent x-ray pictures during convalescent treatment were desirable to determine whether there was osseous involvement.

9. Wang, L. K., and Miltner, L. J.: Chinese M. J. **46**:1, 1932.

10. Ciaccia, S.: Chir. d. org. di movimento **16**:531, 1931.

11. Caldwell, G. A.: Acute Suppurative Conditions of the Hip Joint, J. A. M. A. **98**:37 (Jan. 2) 1932.

## TUBERCULOSIS

*Operative Treatment of Tuberculosis of the Joints.*—Henderson [12] reviewed the present trends in the treatment of tuberculosis of the bones and joints. He stated that conservative treatment has its greatest field of usefulness in children, while operative treatment aiming to ankylose the diseased joints and to eradicate the disease is the treatment of choice in adults. It is important to select the patients for operation carefully, since the results in America are still poor, owing in large part to the unwillingness of patients to continue treatment sufficiently long. Each patient must be studied before the type of treatment can be decided. In general, patients in whom operative treatment is advisable should be beyond the age of puberty, free from active pulmonary tuberculosis and from tuberculosis of the genito-urinary tract and also in good general health. The author advised against extensive operative procedures in the presence of draining sinuses. In a series of more than 600 cases, the operative mortality was less than 1 per cent.

*Liver Meal in the Treatment of Amyloidosis in Surgical Tuberculosis.*—Whitbeck [13] treated 7 patients with amyloid disease following tuberculosis of the bones and joints with liver extract. Powdered whole liver was used and given in doses of 1 drachm (3.9 Gm.) three times daily. Two patients died, 1 from an intercurrent infection and the other from cardiac failure. The other 5 showed benefit three months after therapy had been instituted, and thirteen months later there was distinct improvement, as evidenced by a diminution in the size of the liver and spleen, less anemia, less ascites and improvement in the general state of nutrition. However, in each case the Congo red test was positive at the end of eighteen months, indicating that sufficient lardaceous material was present in the organs to absorb the dye and to remove it completely from the blood.

## POLIOMYELITIS

*Production of Antiviral Substances.*—Howitt,[14] by the injection of poliomyelitis virus into 2 sheep and a goat over a period of years, was able to produce antiviral substances capable of protecting monkeys against infection. The author demonstrated also by a higher percentage of recoveries that the intramuscular route was preferable to the combined intravenous and intrathecal routes in giving convalescent serum to monkeys in the preparalytic stage of poliomyelitis.

*Convalescent Serum in Preparalytic Poliomyelitis.*—In a fairly well controlled group of patients in the preparalytic stage of poliomyelitis in

12. Henderson, M. S.: Minnesota Med. **15**:141, 1932.

13. Whitbeck, B. H.: J. Bone & Joint Surg. **14**:85, 1932.

14. Howitt, B. F.: Proc. Soc. Exper. Biol. & Med. **29**:118, 1931.

southern New England in 1931, Kramer and his co-workers [15] made a careful study of the therapeutic effect of human convalescent poliomyelitic serum given by the combined intraspinous and intravenous routes. The authors were unable to obtain conclusive evidence that the convalescent serum was of value, or, on the other hand, that it was valueless.

*Abortive Poliomyelitis.*—Paul and his associates [16] reported the results of an epidemiologic study of poliomyelitis with particular reference to cases of "abortive" poliomyelitis. By "abortive" poliomyelitis was meant a minor illness showing more or less regular characteristics and occurring during an epidemic of poliomyelitis. The symptomatology of these minor illnesses was not specific, but was essentially that of an acute infection of short duration, symptoms of fever, sore throat, headache and vomiting dominating the picture. A survey of 222 families, in each of which 1 or more cases of poliomyelitis developed, showed that in from 32 to 39 per cent of the other children, i. e., those not coming down with poliomyelitis, minor illness developed coincidentally with the onset of the known cases. In 60 control families studied, it was found that only 9 per cent of the children had minor illnesses during the time of the epidemic. It seemed reasonable to suppose that at least some of the minor illnesses were related to orthodox poliomyelitis. Only if it could be shown that a child became immune subsequent to the development of a minor illness could it be assumed that he had passed through an attack of the disease. This proof awaited further knowledge of the nature of immunity and of the means of measuring it.

*Poliomyelitis in California.*—Meals and Bower [17] reviewed the 1930 epidemic of poliomyelitis in southern California; 350 cases were studied. Spread by "healthy carriers" was frequently observed. The patients were seen, on the average, on the fourth day of the illness. In 11.7 per cent of the cases, paralysis was found on the first examination. In 12.86 per cent, the spinal fluids were negative, but the patients showed characteristic neurologic findings. Twenty-two per cent were negative neurologically, but showed the usual changes in the spinal fluid. Treatment was almost wholly with pooled convalescent serum plus rest and immobilization, with dietetic and eliminative measures. Serum was given, either 15 cc. intrathecally or 30 cc. intramuscularly or intravenously; the mode of administration depended on the severity and the advancement of the disease. The authors preferred the intravenous

15. Kramer, S. D.; Aycock, W. L.; Solomon, C. I., and Thenebe, C. L.: New England J. Med. **206**:432, 1932.

16. Paul, J. R.; Salinger, R., and Trask, J. D.: "Abortive" Poliomyelitis, J. A. M. A. **98**:2262 (June 25) 1932.

17. Meals, R. W., and Bower, A. G.: J. Lab. & Clin. Med. **17**:409, 1932.

or intramuscular administration of serum when there were no phenomena of the central nervous system. In 82 per cent of the cases, the fever abated and the subjective symptoms subsided after the intracisternal injection of serum. In this series there were 60.9 per cent complete recoveries. In 25.66 per cent there was mild residual paralysis, and 10.28 per cent showed more extensive paralyses. The mortality was 3.16 per cent. In the entire country the death rate during this epidemic was 7 per cent.

[ED. NOTE.—The therapeutic effect of convalescent serum in the treatment of preparalytic poliomyelitis is still sub judice. The most carefully controlled observations, although small in number, throw a doubt on the usefulness of the serum. Its use, however, should be encouraged until the matter is settled.]

## ARTHRITIS

*Hemophilic Arthritis.*—Key [18] reported a thorough study of a case of chronic hemophilic arthritis of the knee in which the patient was operated on because of a mistaken diagnosis. Macroscopic and microscopic studies were reported. Key divided hemophilic joints into two types: the acute hemarthrosis and the chronic arthritis. The first type represented the first or early attacks in which the picture was one of intrasynovial hemorrhage, varying in the severity of the symptoms according to the amount of hemorrhage. The second type, a joint into which there had been numerous hemorrhages over a period of years, showed a rather characteristic group of signs and symptoms. Grossly and clinically, this joint simulated almost any of the various types of chronic arthritic lesions. When the lesion was opened, the appearance was characteristic—a thickened, deeply pigmented synovial membrane with a fibrous subsynovial tissue, maplike destruction of the articular cartilage, replaced by either fibrous tissue or unorganized blood clot, and atrophic irregular subchondral osseous structure. A flexion deformity of the joint was frequently seen. Operative intervention was contraindicated; conservative therapy alone should be used. An excellent study of the various types of joints was given, as well as a review of the scant literature on these lesions.

*Syphilitic Arthritis with Effusion.*—Among 112 cases of acute and chronic arthritis with effusion, Kling [19] found that 9 (8.1 per cent) were due to syphilis. All cases showed late manifestations of the disease. Over half of the cases were due to congenital syphilis. Seven showed involvement of the synovial membrane only; 1 patient had a juxta-articular gumma; another had osteochondritis and periostitis.

18. Key, J. A.: Ann. Surg. **95**:198, 1932.
19. Kling, D. H.: Am. J. M. Sc. **183**:538, 1932.

Kling based the diagnosis on (1) the presence of syphilis as shown by the Wassermann reaction of the blood and by other syphilitic lesions, i. e., keratitis and gumma, and (2) examination of the affected joint. He found that complete examination of the fluid of the joint was most important, particularly the Wassermann reaction. He found that a therapeutic test was of value in doubtful cases, always proving of benefit if the diagnosis was correct.

### CIRCULATORY DISTURBANCES

*Raynaud's Disease.*—Allen and Brown [20] studied 150 cases of Raynaud's disease in order to determine the minimal requisites for diagnosis. They found that the symptoms described by Raynaud were necessary for a diagnosis. These were: gangrene or trophic disturbances limited almost wholly to the skin, symmetrical or bilateral involvement, absence of evidence of any occlusive lesions of the peripheral arteries and intermittent attacks.

*Deep Ligation of the Vein for Gangrene.*—Pearse [21] reported the results of deep ligation of the vein in 20 cases of diabetic and arteriosclerotic gangrene. Thirty-one additional cases from the literature were reviewed. Ligation of the external iliac vein, the femoral vein or the popliteal vein was done. Of 20 patients so treated, the results in 8 were successful, the results in 8 were failures, and 4 patients died within a year without amputation. The cases were divided into 3 classes: (1) cases in which amputation of the leg should be done; (2) those in which amputation should not be done, and (3) borderline cases. The beneficial results from ligation of the vein were warmth, diminution of pain and objective changes in the limb. Edema rarely occurred. Additional factors in the treatment of such limbs were enumerated in a discussion of the preoperative and the postoperative treatment.

20. Allen, E. V., and Brown, G. E.: Am. J. M. Sc. **183**:187, 1932.

21. Pearse, H. E.: The Use of Vein Ligation in the Treatment of Arteriosclerotic and Diabetic Gangrene, J. A. M. A. **98**:866 (March 12) 1932.

*(To be Concluded)*